Synthesis of a Highly Functionalised and Homochiral 2-Iodocyclohexenone Related to the C-Ring of the Polycyclic, Indole Alkaloids Aspidophytine and Haplophytine

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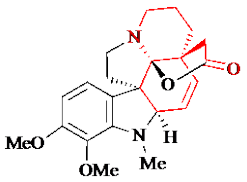

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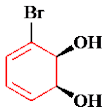

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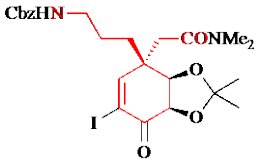

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ABSTRACT: The enzymatically-derived and enantiomerically pure (1*S*,2*S*)-3-bromocyclohexa-3,5-diene-1,2-diol (**7**) has been elaborated over ten steps into cyclohexenone **8**. The latter compound embodies the enantiomeric form of the C-ring associated with the hexacyclic framework of the alkaloid aspidophytine (**2**). As such, this work sets the stage for effecting the conversion of the enantiomeric metabolite *ent*-**7** into compound *ent*-**8**, and thence, through previously established protocols including a palladium-catalysed Ullmann cross-coupling reaction, into the title alkaloids.

INTRODUCTION

The hetero-dimeric indole alkaloid haplophytine (**1**)[1-3] (Figure 1) is, as confirmed by X-ray analysis,[2] a structurally distinctive metabolite derived from the Central American plant *Haplophyton cimicidum*, the dried leaves of which were first employed by the Aztecs for insecticidal purposes.[1] The right-hand segment of compound **1** embodies the aspidophytine framework **2** that is itself obtained from *Haplophyton crooksii* (a.k.a. the cockroach plant) found in the Southern US as well as the north of Mexico. It too is used as an insecticide, especially against cockroaches.[3]

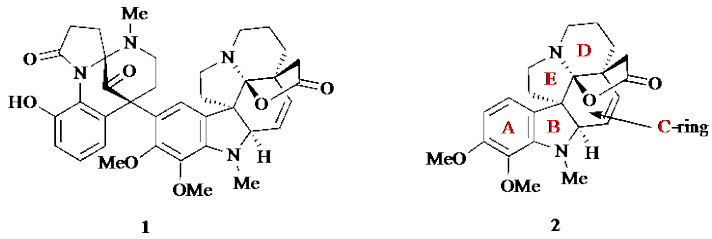
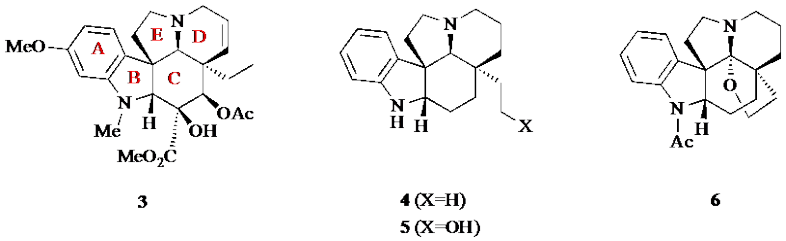


Figure 1: The structures of haplophytine (**1**) and aspidophytine (**2**)

The elaborate molecular architectures of haplophytine (**1**) and aspidophytine (**2**) have prompted a range of synthetic studies. In 1999 Corey and his co-workers reported the first assembly of (–)-aspidophytine.[4] Subsequently, Fukuyama (2003), Padwa (2006), Marino (2006), Nicolaou (2008), Tokuyama (2013) and Qiu (2013)[5] achieved the same target. Even more dramatically, after years of sustained effort by many groups, total syntheses of haplophytine (**1**) were reported, contemporaneously in 2009, by the Fukuyama/Tokuyama[6] and the Nicolaou/Chen[7] groups.[8] In 2016, and inspired by earlier biosynthetic proposals, Tokuyama and co-workers were able to couple an advanced precursor to aspidophytine (**2**) with one associated with the left-hand segment of compound **1**.[9] By such means, and after conducting a key, one-pot aerobic oxidation/skeletal rearrangement cascade, the completion of a more convergent total synthesis of haplophytine was realized.

Our own interest in constructing various Aspidosperma alkaloids has resulted in the establishment of methods for assembling a close structural analogue of vindoline (**3**)[10] as well as total syntheses of the racemic modifications of aspidospermidine (**4**),[11]

limaspermidine (**5**)[12] and its oxidative cyclisation product 1-acetylaspidoalbidine (**6**)[12] (Figure 2). The analogue of vindoline was obtained in enantiomerically pure form as a result of employing a homochiral and enzymatically-derived *cis*-1,2-dihydrocatechol as the starting material.[10,13] Compounds **3**-**6** each embody an ABCDE-ring system that is enantiomerically related to the one seen in aspidophytine (**2**) while the last of these, *viz*. **6**, also incorporates the tetrahydrofuran substructure. A key step associated with all of these syntheses was the palladium-catalyzed Ullmann cross-coupling of a 2-iodocyclohexenone with an *o*-iodinated nitroarene.[14] This was followed by reductive cyclization of the resulting 2-arylated cyclohexenone, often using dihydrogen in the presence of Raney-cobalt.[15] The piperidine-annulated tetrahydrocarbazoles so-formed were each be subjected to an annulation protocol developed by Heathcock and co-workers[16] and thus completing the assembly of the ABCDE-ring system associated with compounds **3**-**6**.



3 **4** (X=H) **5** (X=OH) **6**

Figure 2: The structures of vindoline (**3**), aspidospermidine (**4**), limaspermidine (**5**) and 1-acetylaspidoalbidine (**6**)

We are now seeking to apply our earlier work in developing total syntheses of the title alkaloids. As part of this program, we report herein the conversion of the readily obtained and homochiral *cis*-1,2-dihydrocatechol **7**[13] (Figure 3) into the 2-iodocyclohexenone **8** that embodies key elements associated the C-ring of *ent*-aspidophytine (*ent*-**2**). Given that compound *ent*-**7** is also available,[17] albeit less readily, this work should eventually allow for the synthesis of compounds **1** and **2** as well as their optical antipodes.

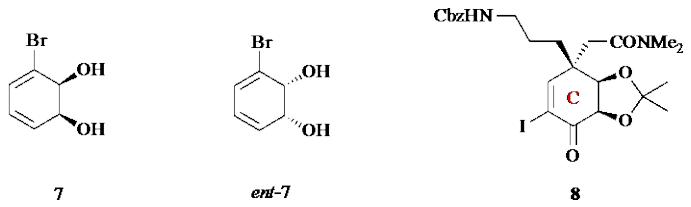
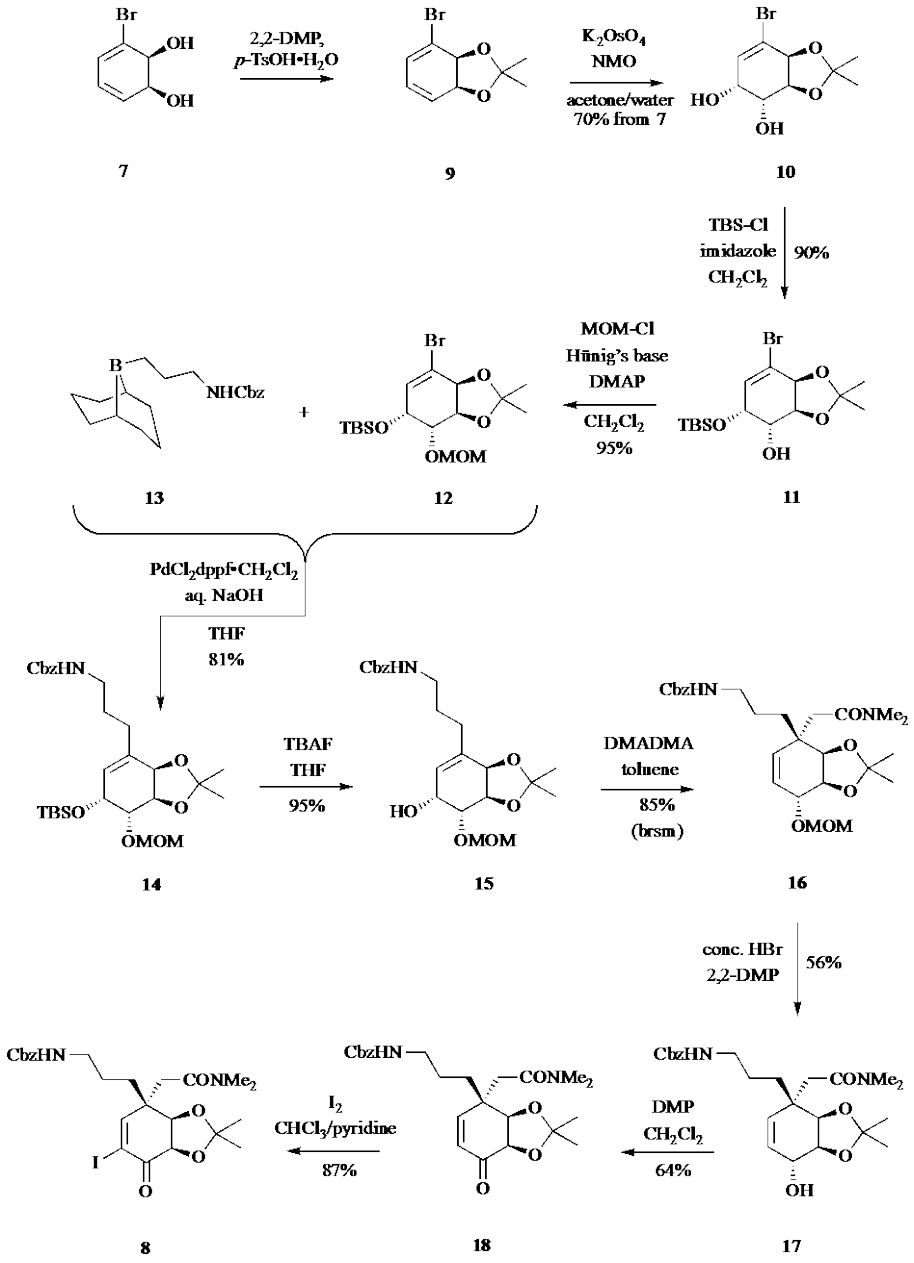


Figure 3: The structure of the homochiral starting material **7**, its enantiomer (*ent*-**7**) and the target 2-iodocyclohexenone **8**

RESULTS AND DISCUSSIONS

The route employed in the synthesis of target **8** is shown in Scheme 1. This starts with the conversion of diol **7**, using 2,2-dimethoxypropane (2,2-DMP) in the presence of catalytic quantities of *p*-toluenesulfonic acid monohydrate (*p*-TsOH•H_2O), into the corresponding and known acetonide **9**.[10] Given that the latter compound shows a ready propensity to engage in a Diels-Alder dimerization reaction,[18] it was immediately subjected to a regio- and diastereo-selective dihydroxylation reaction using K_2OsO_4•$2H_2O$ as the catalytic oxidant and *N*-methylamine *N*-oxide (NMO) as the stoichiometric one.[19] This resulted in the formation of the bromoconduritol mono-acetonide **10**[10] (70% from **7**). The more accessible allylic hydroxyl group associated with compound **10** could be selectively protected using *tert*-butyldimethylsilyl chloride (TBS-Cl) in the presence of imidazole and thus providing the mono-ether **11**[10] in 90% yield. Treatment of compound **11** with chloromethyl methyl ether (MOM-Cl) in the presence of Hünig's base (*N*,*N*-diisopropylethylamine) and 4-(*N*,*N*-dimethylamino)pyridine (DMAP) then gave product **12**[10] in 95% yield. Suzuki-Miyaura cross-coupling of the bromocyclohexene **12** with the previously unreported, 9-BBN-derived carbamate **13** (readily prepared *in situ* from 9-BBN and benzyl allylcarbamate) gave the anticipated product **14** (91%). On treating compound **14** with tetra-*n*-butylammonium fluoride (TBAF) desilylation took place to give the allylic alcohol **15** (95%). In a critical step of the reaction sequence, compound **15** was readily engaged in an Eschenmoser-Claisen rearrangement[10,12,20] on treatment with dimethylacetamide dimethyl acetal (DMADMA) in refluxing toluene and so cleanly producing the allylic ether **16** (85%).

Scheme 1: Conversion of metabolite **7** into the target 2-iodocyclohexenone **8**.



Significantly, compound **16** incorporates one of the two quaternary carbon centers associated with the enantiomeric form of the C-rings of the alkaloids haplophytine (**1**) and aspidophytine (**2**). As implied above, the correct configuration at this stereogenic center, and from which the ones at the others automatically follow,[11,12] could be established by using metabolite *ent*-**7** (rather than **7**) as the starting material in this sequence.

The conversion of compound **16** into target **8** involved three additional steps, the first of which was the cleavage of the MOM-ether. This was achieved using concentrated aqueous HBr at ambient temperatures. To prevent accompanying hydrolysis of the associated acetonide unit, this reaction was run in 2,2-DMP. As a result the allylic alcohol **17** was obtained, albeit in just 56% yield. Oxidation of compound **17** was best effected with the Dess-Martin periodinane (DMP)[21] and resulted in the formation of enone **18** (64%). Subject of the latter compound to a Johnson α-iodination reaction[22] then provided target **8** in 87% yield. All of the spectral data acquired on compound **8** were in complete accord with the assigned structure. In particular, a molecular-associated ion (M+H) was observed in the electrospray ionization mass spectrum and an accurate mass measurement on this species established it was of the required composition, *viz*. $C_{24}H_{31}IN_2O_6$. In the ^{13}C NMR spectrum the expected twenty-two signals were observed while in the infrared spectrum carbonyl absorption bands were observed at 1697 and 1633 cm^{-1}.

CONCLUSIONS

The reaction sequence detailed here will allow for the conversion of the homochiral metabolite *ent*-**7** into the cyclohexenone *ent*-**8**. Furthermore, our earlier studies on the synthesis of aspidopsermidine (**4**),[11] limaspermidine (**5**)[12] and 1-acetylaspidoalbidine (**6**),[12] will inform us as to effective methods for the elaboration of compound *ent*-**8** into the structurally related aspidophytine (**2**) and even, perhaps, the more elaborate haplophytine (**1**). The conversion *ent*-**8** $\rightarrow$ **2** is likely to involve, in the first stages, a palladium-catalysed Ullmann cross-coupling reaction so as to install the required dimethoxyaryl group and the associated nitrogen. Subsequent hydrogenolysis and reductive cyclisation steps leading to the B- and D-rings are likely to follow. A Heathcock annulation (to install the E-ring) and an oxidative cyclisation reaction (involving an angular acetic acid group) to form the lactone ring would then be deployed. At some point the acetonide residue associated with compound *ent*-**8** will need to be converted into the corresponding cyclohexene and this is most likely to involve a Corey-Winter olefin synthesis.[20b] Efforts directed towards such ends will be reported in due course.

EXPERIMENTAL SECTION

General Experimental Procedures. Unless otherwise specified, proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded at room temperature in base-filtered $CDCl_3$ on a spectrometer operating at 400 MHz for proton and 101 MHz for carbon nuclei. The signal due to residual $CHCl_3$ appearing at δ_H 7.26 and the central resonance of the $CDCl_3$ "triplet" appearing at δ_C 77.0 were used to reference ^{1}H and ^{13}C NMR spectra, respectively. ^{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. Infrared spectra (ν_{max}) were recorded on an ATR-FTIR spectrometer. Samples were analyzed in neat form. Optical rotations were recorded in the indicated solvent at 22 °C. Low-resolution ESI mass spectra were recorded on a single quadrupole liquid chromatograph-mass spectrometer while high-resolution measurements were conducted on a time-of-flight instrument. Analytical thin layer chromatography (TLC) was performed on aluminum-backed 0.2 mm thick silica gel 60 F_{254} plates. Eluted plates were visualized 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 (conc.) : 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). Flash chromatographic separations were carried out following protocols defined by Still *et al*.[23] with silica gel 60 (40–63 μm) as the stationary phase and using the AR- or HPLC-grade solvents indicated. Starting materials, reagents, drying agents, and other inorganic salts were generally commercially available and used as supplied. Tetrahydrofuran (THF), methanol and dichloromethane were dried using a solvent purification system that is based upon a technology originally described by Grubbs *et al*.[24] Where necessary, reactions were performed under an atmosphere of nitrogen.

Specific Chemical Transformations

(3a*S*,7a*S*)-4-Bromo-2,2-dimethyl-3a,7a-dihydrobenzo[*d*][1,3]dioxole (9). A magnetically stirred solution of compound **7**[13b] (4.78 g, 25.0 mmol) in 2,2-dimethoxypropane (50 ml) was treated with *p*-TsOH•H_2O (43 mg, 0.23 mmol, 1 mole %) and the ensuing mixture stirred at 22 °C for 2 h then concentrated, without heating, under reduced

pressure. The residue thus obtained was dissolved in ethyl acetate/CH_2Cl_2 (100 mL of a 1:1 v/v mixture) and the resulting solution washed with water (2 × 30 mL) before being dried (Na_2SO_4), filtered then concentrated under reduced pressure (no heating) to give the compound **9**[10,18] (ca. 5.75 g) as a light-brown oil. This material was used immediately in the next step of the reaction sequence.

(3a*S*,4*R*,5*R*,7a*S*)-7-Bromo-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxole-4,5-diol (10). A magnetically stirred solution of the crude acetonide **9** (*ca*. 5.75 g, 24. 9 mmol, 1.0 mole eq.) in acetone/water (100 ml of a 4:1 v/v mixture) was cooled to 0 °C then treated with K_2OsO_4•$2H_2O$ (158 mg, 0.25 mmol, 0.01 mole eq.) and NMO (6.41 g, 54.8 mmol, 2.2 mole eq). The ensuing mixture was allowed to warm to 22 °C then stirred at this temperature for 16 h before being diluted with ethyl acetate (50 mL). The separated aqueous layer was extracted with ethyl acetate (3 × 30 mL) and the combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was subjected to flash column chromatography (silica, 3:7 v/v ethyl acetate/40-60 petroleum spirits elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3 in 2:3 v/v ethyl acetate/40-60 petroleum spirits), the title diol **10**[10] (4.67 g, 70 % over 2 steps) as a light-brown solid, m.p. = 112 °C, $[\alpha]_D$ = –4.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 6.16 (broadened s, 1H), 4.66 (m, 1H), 4.45 (t, *J* = 5.4 Hz, 1H), 4.36 (broadened s, 1H), 4.19 (t, *J* = 4.6 Hz, 1H), 2.53 (s, 2H), 1.44 (s, 3H), 1.41 (s, 3H); ^{13}C NMR δ 131.1, 123.9, 110.5, 76.5, 76.4, 69.6, 67.4, 27.8, 26.3; IR (ATR) ν_{max} 3401, 2987, 2934, 1645, 1382, 1373, 1229, 1079, 1050, 856, 628 cm^{-1}; MS (ESI, +ve) *m/z* 289 and 287 [$(M+Na)^+$, 95 and 100%]; HRMS $(M+Na)^+$, calcd for $C_9H_{13}{}^{79}BrO_4Na$ 286.9889, found: 286.9880.

(3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-5-((*tert*-butyldimethylsilyl)oxy)-2,2-dimethyl-3a,4,5,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-ol (11). A suspension of compound **10** (8.00 g, 30.2 mmol) in CH_2Cl_2 (100 ml) was maintained at 0 °C then imidazole (5.28 g, 77.6 mmol, 2.56 mole eq.) and TBS-Cl (8.19 g, 54.3 mmol, 1.8 mole eq.) added to it. The ensuing mixture was stirred at 22 °C for 1 h then quenched with water (50 mL). The separated aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL) and the combined organic phases then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue so obtained was subjected to flash column chromatography (silica, 1:15 v/v ethyl acetate/40-60 petroleum spirits elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.6 in 1:9 v/v ethyl acetate/40-60 petroleum spirits), ether **11**[10] (10.34 g,

90%) as a light-yellow solid, m.p. = 85 °C, $[\alpha]_D$ = –32.0 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 5.91 (m, 1H), 4.62 (m, 1H), 4.49 (t, *J* = 4.8 Hz, 1H), 4.37 (m, 1H), 4.16 (m, 1H), 2.62 (d, *J* = 1.7 Hz, 1H), 1.43 (s, 3H), 1.40 (s, 3H), 0.92 (s, 9H), 0.15 (s 3H), 0.13 (s 3H); ^{13}C NMR δ 130.8, 123.6, 110.1, 76.1, 75.8, 69.3, 68.2, 27.7, 26.3, 25.9, 18.2, –4.5, –4.7; IR (ATR) ν_{max} 3558, 2988, 2952, 2929, 2857, 1646, 1471, 1370, 1076, 1052, 865, 837, 777, 681 cm^{-1}; MS (ESI, +ve) *m/z* 403 and 401 [$(M+Na)^+$, 98 and 100%]; HRMS $(M+Na)^+$, calcd for $C_{15}H_{27}{}^{79}BrO_4SiNa$ 401.0760, found: 401.0761.

(((3a*S*,4*S*,5*R*,7a*S*)-7-Bromo-4-(methoxymethoxy)-2,2-dimethyl-3a,4,5,7a-tetrahydro-benzo[*d*][1,3]dioxol-5-yl)oxy)(*tert*-butyl)dimethylsilane (12). A magnetically stirred solution of compound **11** (1.00 g, 2.64 mmol) in CH_2Cl_2 (5 mL) maintained at 0 °C was treated with DMAP (322 mg, 2.63 mmol, 1.0 mole eq.) then Hünig's base (2.7 mL, 15.8 mmol, 6.0 mole eq.) and MOM-Cl[25] (2.1 mL, 19.8 mmol, 7.5 mole eq.). The ensuing mixture was stirred at 22 °C for 16 h before being quenched with NH_4Cl (30 mL of a saturated aqueous solution) and the separated aqueous phase extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The reside thus obtained were subjected to flash column chromatography (silica, 1:19 v/v ethyl acetate/40-60 petroleum spirits elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.5), the title compound **12**[10] (1.06 g, 95%) as a colourless, semi-solid, $[\alpha]_D$ = –71.4 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 6.06 (broadened s, 1H), 4.82 (d, *J* = 6.7 Hz, 1H), 4.72 (d, *J* = 6.7 Hz, 1H), 4.65 (d, *J* = 5.5 Hz, 1H), 4.47 (m, 2H), 4.08 (m, 1H), 3.40 (s, 3H), 1.43 (s, 3H), 1.40 (s, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H); ^{13}C NMR δ 132.8, 122.6, 110.3, 97.3, 77.0, 76.0, 75.6, 68.1, 55.9, 27.7, 26.4, 25.9, 18.3, –4.6 (one signal obscured or overlapping); IR (ATR) ν_{max} 2988, 2953, 2930, 1644, 1464, 1381, 1371, 1253, 1133, 1115, 1078, 1037, 865, 776, 680 cm^{-1}; MS (ESI, +ve) *m/z* 447 and 445 [$(M+Na)^+$, 99 and 100%]; HRMS $(M+Na)^+$, calcd for $C_{17}H_{31}{}^{79}BrO_5SiNa$ 445.1022, found: 445.1019.

Benzyl (3-((1*s*,5*s*)-9-Borabicyclo[3.3.1]nonan-9-yl)propyl)carbamate (13). Following a protocol reported by Rychnovsky,[26] benzyl allylcarbamate[27] (500 mg, 2.61 mmol) was added to magnetically stirred 9-BBN (5 mL of a 0.5 M solution in THF, 2.5 mmol) maintained at 22 °C. Stirring was continued at this temperature for 16 and the solution thus obtained, and presumed to contain compound **13**, used directly in the Suzuki-Miyaura cross-coupling with compound **12** as detailed immediately below.

Benzyl (3-((3a*R*,6*R*,7*S*,7a*R*)-6-((*tert*-Butyldimethylsilyl)oxy)-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)propyl)carbamate (14). A sol- ution of compound **13** (1.04 mL of a 0.5 M solution in THF, 0.52 mmol), prepared as described immediately above, was dissolved THF (1.5 ml) containing NaOH (2.3 mL of a 3 M aqueous solution). The ensuing mixture was stirred magnetically at 22 °C for 0.3 h then added into a magnetically stirred solution of compound **12** (200 mg, 0.47 mmol, 1.0 mole eq.) in THF (1 mL) maintained at 22 °C. The resulting mixture was deoxygenated with nitrogen then $PdCl_2$dppf·CH_2Cl_2 (40 mg, 0.05 mmol, 10 mole %) was added. The mixture thus obtained was stirred at 22 °C under nitrogen for 16 h before being quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution). The separated aqueous layer was extracted with ethyl acetate (3 × 15 mL) and the combined organic phases then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, 1:4 v/v ethyl acetate/40-60 petroleum spirits elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.4), carbamate **14** (243 mg, 81%) as a clear, colourless oil, $[\alpha]_D$ = –72.7 (*c* 0.83, $CHCl_3$). ^{1}H NMR δ 7.41-7.26 (complex m, 5H), 5.51 (broadened s, 1H), 5.09 (s, 2H), 4.94 (broad s, 1H), 4.78 (d, *J* = 6.6 Hz, 1H), 4.71 (d, *J* = 6.6 Hz, 1H), 4.52 (d, *J* = 6.0 Hz, 1H), 4.41 (t, *J* = 6.0 Hz, 1H), 4.35 (t, *J* = 3.7 Hz, 1H), 3.87 (m, 1H), 3.37 (s, 3H), 3.22 (m, 2H), 2.18 (m, 2H), 1.73 (m, 2H), 1.38 (s, 3H), 1.36 (s, 3H), 0.89 (s, 9H), 0.09 (s, 3H), 0.07 (s, 3H); ^{13}C NMR δ 156.5, 137.2, 136.8, 128.6, 128.2(3), 128.1(7), 126.2, 109.2, 96.3, 76.3, 75.1, 74.6, 66.7, 66.5, 55.6, 40.9, 31.2, 27.7, 27.6, 26.0(2), 25.9(6), 18.3, –4.4, –4.6; IR (ATR) ν_{max} 3349, 2929, 2857, 1709, 1525, 1472, 1246, 1031, 885, 775 cm^{-1}; MS (ESI, +ve) *m/z* 558 [(M+Na)$^+$, 100%]; HRMS (M+Na)$^+$, calcd for $C_{28}H_{45}NO_7SiNa$ 558.2863, found: 558.2864.

Benzyl (3-((3a*R*,6*R*,7*R*,7a*R*)-6-Hydroxy-7-(methoxymethoxy)-2,2-dimethyl-3a,6,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)propyl)carbamate (15). A magnetically stirred solution of compound **14** (3.19 g, 5.95 mmol) in THF (14 mL) was cooled to 0 °C then treated with TBAF (12.4 mL of a 0.5 M solution in THF, 1.05 mole eq.). The ensuing mixture was allowed to warm to 22 °C over 2 h and stirring continued at this temperature for 16 h. The reaction mixture was then diluted with $NaHCO_3$ (20 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 15 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under

reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 4:6 → 7:3 → 8:2 v/v ethyl acetate/40-60 petroleum spirits gradient elution). Concentration of the appropriate fractions (R_f = 0.2 in 1:1 v/v ethyl acetate/40-60 petroleum elution) then gave allylic alcohol **15** (2.40 g, 95 %) as a clear, colourless oil, $[\alpha]_D$ = –35.7 (*c* 0.48, $CHCl_3$). ^{1}H NMR δ 7.41-7.27 (complex m, 5H), 5.63 (broadened s, 1H), 5.09 (s, 2H), 4.90 (broad s, 1H), 4.77 (m, 2H), 4.51 (d, *J* = 6.2 Hz, 1H), 4.43 (m, 1H), 4.35-4.24 (broadened s, 1H), 3.87 (m, 1H), 3.40 (s, 3H), 3.23 (m, 2H), 2.68 (d, *J* = 6.1 Hz, 1H), 2.22 (m, 2H), 1.74 (m, 2H), 1.40 (s, 3H), 1.37 (s, 3H); ^{13}C NMR δ 156.5, 138.3, 136.7, 128.6, 128.2(1), 128.1(8), 125.0, 109.5, 96.9, 78.0, 74.8, 74.5, 66.7, 65.5, 55.8, 40.8, 31.1, 27.8, 27.4, 26.1; IR (ATR) ν_{max} 3348, 2985, 2934, 1699, 1531, 1455, 1380, 1240, 1027, 916, 698 cm^{-1}; MS (ESI, +ve) *m/z* 444 [$(M+Na)^+$, 100%]; HRMS $(M+Na)^+$, calcd for $C_{22}H_{31}NO_7Na$ 444.1998, found: 444.1192.

Benzyl (3-((3a*R*,4*S*,7*R*,7a*S*)-4-(2-(Dimethylamino)-2-oxoethyl)-7-(methoxymethoxy)-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)propyl)carbamate (16). A magnetically stirred solution of compound **15** (1.86 g, 4.41 mmol,) in toluene (23 mL) was treated with DMADMA (6.0 mL, 39.7 mmol, 9 mole eq.) and the ensuing mixture heated under reflux for 1 h before being cooled to 90 °C and the reaction vessel vented for 0.5 h so as to allow the by-product methanol to evaporate. The reaction mixture was then heated again under reflux for 1 h, cooled to 90 °C and vented once more for 0.5 h. Further DMADMA (3.0 mL, 19.9 mmol, 4.5 mole eq.) was added to the reaction mixture that was then heated under reflux for 16 h. The cooled reaction mixture was concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, 7:3 v/v ethyl acetate/40-60 petroleum spirits elution) and so affording two fractions, A and B.

Concentration of fraction A (R_f = 0.2 in 1:1 v/v ethyl acetate/40-60 petroleum spirits) afforded allylic alcohol **15** (290 mg, 16% recovery) as a clear, colourless oil that was identical, in all respects, with an authentic sample.

Concentration of fraction B (R_f = 0.2 in 1:4 v/v ethyl acetate/diethyl ether) afforded compound **16** (1.55 g, 72% or 85% brsm), as a white, crystalline solid m.p. = 84 °C, $[\alpha]_D$ = –18.3 (*c* 1.0, $CHCl_3$). ^{1}H NMR δ 7.36-7.20 (complex m, 5H), 5.75 (m, 2H), 5.09 (s, 2H), 5.03 (broad s, 1H), 4.81 (d, *J* = 6.7 Hz, 1H), 4.72 (d, *J* = 6.7 Hz, 1H), 4.31 (s, 2H), 4.19 (s, 1H), 3.39 (s, 3H), 3.16 (m, 2H), 3.01 (s, 3H), 2.91 (s, 3H), 2.50 (m, 2H),

1.76-1.48 (complex m, 3H), 1.41 (s, 3H), 1.33 (s, 3H); ^{13}C NMR δ 170.5, 156.5, 136.8, 135.9, 128.5, 128.1, 128.0, 125.8, 108.2, 95.5, 79.3, 78.2, 74.4, 66.5, 55.5, 41.6, 40.8, 39.1, 37.9, 35.5, 31.8, 26.8, 24.9, 24.2; IR (ATR) ν_{max} 3332, 2936, 1717, 1635, 1525, 1455, 1240, 1041, 731 cm^{-1}; MS (ESI, +ve) *m/z* 513 [(M+Na)$^+$, 100%]; HRMS (M+Na)$^+$, calcd for $C_{26}H_{38}N_2O_7Na$ 513.2577, found: 513.2578.

Benzyl (3-((3a*R*,4*S*,7*R*,7a*S*)-4-(2-(dimethylamino)-2-oxoethyl)-7-hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)propyl)carbamate (17). A magnetically stirred solution of compound **16** (47 mg, 0.09 mmol) in 2,2-DMP (1.6 mL) was cooled to 0 °C then treated with HBr (5 drops of a 48% aqueous solution). The reaction mixture was kept at 0 °C for 0.1 h then warmed to 22 °C, maintained at this temperature for 1.5 h then quenched with $NaHCO_3$ (5 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 5 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue thus obtained was subjected to flash column chromatography (silica, ethyl acetate eltuion) and thus affording, after concentration of the appropriate fractions (R_f = 0.2) compound **17** (24 mg, 56%) as a clear, colourless oil, $[\alpha]_D$ = –33.8 (*c* 1.07, $CHCl_3$). ^{1}H NMR δ 7.45-7.28 (complex m, 5H), 5.75 (m, 1H), 5.68 (m, 1H), 5.09 (s, 2H), 4.96 (broad s, 1H), 4.35 (d, *J* = 7.3 Hz, 1H), 4.29 (dd, *J* = 7.3 and 3.9 Hz, 1H), 4.22 (broadened s, 1H), 3.17 (m, 2H), 3.01 (s, 3H), 2.91 (s, 3H), 2.55 (s, 2H), 2.46 (d, *J* = 6.2 Hz, 1H), 1.55 (broadened s, 4H), 1.41 (s, 3), 1.34 (s, 3H); ^{13}C NMR δ 170.9, 156.5, 136.8, 134.6, 128.6, 128.2, 128.1, 128.0, 108.1, 81.0, 78.3, 69.8, 66.6, 41.6, 41.0, 40.0, 38.0, 35.6, 32.9, 26.9, 25.0, 24.4; IR (ATR) ν_{max} 3338, 2978, 2934, 1705, 1627, 1527, 1241, 1045, 752, 698 cm^{-1}; MS (ESI, +ve) *m/z* 469 [(M+Na)$^+$, 100%]; HRMS (M+Na)$^+$, calcd for $C_{24}H_{34}N_2O_6Na$ 469.2315, found: 469.2307.

Benzyl (3-((3a*R*,4*S*,7a*R*)-4-(2-(Dimethylamino)-2-oxoethyl)-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)propyl)carbamate (18). A magnetically stirred solution of compound **17** (41 mg, 0.09 mmol) in CH_2Cl_2 (3 mL) maintained at 0 °C under a nitrogen atmosphere was treated with DMP (98 mg, 0.23 mmol, 2.5 mole eq.). The ensuing mixture was allowed to stir at 0 °C for 0.1 h then at 22 °C temperature for 16 h before being quenched with $NaHCO_3$ (2 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 3 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue

thus obtained was subjected to flash column chromatography (silica, ethyl acetate elution) and thus affording, after concentration of the appropriate fractions (R_f = 0.3), enone **18** (26 mg, 64%), as a clear, colourless oil, $[\alpha]_D$ = –13.7 (*c* 0.9, $CHCl_3$). ^{1}H NMR δ 7.47-7.25 (complex m, 5H), 6.80 (d, *J* = 10.4 Hz, 1H), 6.05 (d, *J* = 10.4 Hz, 1H), 5.09 (s, 2H), 4.99 (broad s, 1H), 4.48 (s, 2H), 3.20 (q, *J* = 6.5 Hz, 2H), 2.97 (s, 3H), 2.90 (s, 3H), 2.58 (m, 2H), 1.81 (m, 1H), 1.63 (m, 3H), 1.36 (s, 3H), 1.32 (s, 3H); ^{13}C NMR δ 196.0, 169.2, 156.5, 154.8, 136.7, 128.6, 128.2(3), 128.2(1), 126.4, 109.5, 78.7, 75.1, 66.7, 41.4, 41.2, 40.4, 38.1, 35.7, 33.4, 27.3, 25.8, 23.8; IR (ATR) ν_{max} 3347, 2984, 2935, 1717, 1684, 1637, 1372, 1237, 1044, 698 cm^{-1}; MS (ESI, +ve) *m/z* 467 [(M+Na)$^+$, 100%]; HRMS (M+Na)$^+$, calcd for $C_{24}H_{32}N_2O_6Na$ 467.2158, found: 467.2159.

Benzyl (3-((3a*R*,4*S*,7a*R*)-4-(2-(Dimethylamino)-2-oxoethyl)-6-iodo-2,2-dimethyl-7-oxo-3a,4,7,7a-tetrahydrobenzo[*d*][1,3]dioxol-4-yl)propyl)carbamate (8). A magnetically stirred solution of compound **18** (72 mg, 0.16 mmol) in chloroform/pyridine (10 ml of a 1:1 v/v mixture) was treated with molecular iodine (226 mg, 0.89 mmol, 5.5 mole eq.) and the resulting mixture stirred at 22 °C for 16 h then quenched with Na_2SO_3 (10 mL of a saturated aqueous solution) and the separated aqueous layer extracted with ethyl acetate (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered and concentrated under reduced pressure and the residue thus obtained subjected to flash column chromatography (silica, ethyl acetate elution). Concentration of the appropriate fractions (R_f = 0.5) afforded compound **8** (80 mg, 87%) as a clear, colourless oil, $[\alpha]_D$ = –75.6 (*c* 0.8, $CHCl_3$). ^{1}H NMR δ 7.49 (s, 1H), 7.42-7.27 (complex m, 5H), 5.10 (s, 2H), 4.96 (broad s, 1H), 4.66 (d, *J* = 5.3 Hz, 1H), 4.51 (d, *J* = 5.3 Hz, 1H), 3.21 (m, 2H), 2.98 (s, 3H), 2.89 (s, 3H), 2.56 (m, 2H), 1.88 (m, 1H), 1.77 (m, 1H), 1.63 (m, 2H), 1.36 (s, 3H), 1.29 (s, 3H); ^{13}C NMR δ 189.8, 168.8, 162.4, 156.5, 136.7, 128.6, 128.2(0), 128.1(5), 109.7, 100.0, 78.9, 74.2, 66.7, 45.4, 41.2, 40.3, 38.0, 35.7, 33.4, 27.3, 25.7, 23.8; IR (ATR) ν_{max} 3348, 2985, 2934, 1697, 1633, 1522, 1454, 1238, 1078, 1044, 749 cm^{-1}; MS (ESI, +ve) *m/z* 593 [(M+Na)$^+$, 100%]; HRMS (M+H)$^+$, calcd for $C_{24}H_{32}IN_2O_6Na$ 571.1300, found: 571.1301.

ASSOCIATED CONTENT

Supplementary Material

^{1}H and ^{13}C NMR spectra for compounds **10-18** and **8**. This material is available free of charge via the Internet at XXXXXX.

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Notes

The authors declare no competing financial interest

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Graphical Abstract Text:

The synthesis of a homochiral 2-iodocyclohexenone related to the C-ring of the title alkaloids is reported.

Graphical Abstract: