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# A chemoenzymatic total synthesis of *ent*-narciclasine

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**Abstract**

The synthesis of the title compound [(−)-**1**] has been achieved, for the first time, by reacting the aryl boronic acid ester **4** with the aminoconduritol derivative **6** under Suzuki–Miyaura cross-coupling conditions then subjecting the product phenanthridinone **23** to a global deprotection process using trimethylsilyl bromide. The aromatic building block **4** was prepared in ten steps from piperonal while compound **6** was obtained in nine steps from the enantiomerically pure *cis*-1,2-dihydrocatechol **7**. This last compound is available, in multi-gram quantities, through a whole-cell-mediated biotransformation of bromobenzene using genetically engineered organisms that over-express the responsible enzyme, namely toluene dioxygenase. Since the enantiomer of compound **7** is available by related means, the present work also represents a formal total synthesis of the alkaloid narciclasine [(+)-**1**]. The single-crystal X-ray analysis of compound **13** is reported.
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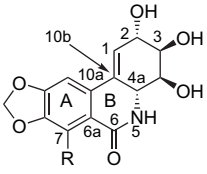
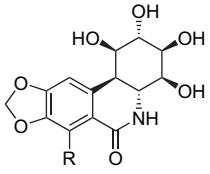
## 1. Introduction

Narciclasine [(+)-**1**, a.k.a. lycoricidinol] is an *Amaryllidaceae* alkaloid that has been isolated from various Narcissus species including *Narcissus incomparabilis Mill.*[1] It is structurally related to lycoricidine [(+)-**2**] and pancratistatin [(+)-**3**], which have been obtained from the same and/or similar sources. All three alkaloids display a range of potentially useful biological properties that have ensured that they continue to attract attention more than four decades after the first of them was identified in nature.[1]




(+)-**1** R=OH
(+)-**2** R=H




(+)-**3**

Ceriotti in Italy described the antimitotic activity of narciclasine [(+)-**1**] in 1967[2] while, in the following year, a Japanese group identified a natural product that they named lycoricidinol and which was shown to possess carcinostatic properties as well as a capacity to exert a strong growth-inhibiting action on rice seedlings.[3] Shortly thereafter it was established that narciclasine and lycoricidinol were one and the same compound.[4] In 1972, and after some initial errors,[4,5] the true structure of (+)-narcicasine was established through a series of synthetic, biosynthetic and X-ray crystallographic studies.[6] The biological properties of narciclasine have continued to be investigated since this time and it has been established that the compound inhibits the growth of the pathogenic yeast *Cryptococcus neofroms* while certain derivatives act against the pathogenic bacterium *Neisseris gonorrhoeae*.[7] The compound has also been found to inhibit the cytotoxic properties of calprotectin, a protein found in neutrophils and in extracellular media during inflammation.[8] It is ten times more active, in this respect, than the alkaloids lycorine, ungerine and hippeastrine. Some insect antifeedant properties have also been ascribed to narciclasine[9] while certain, naturally-occurring glycoslyated derivatives have been shown to possess cytotoxic and antitumour activity very similar to the parent alkaloid.[10]

The biological properties and novel structural features associated with narciclasine have ensured that the compound has continued to receive attention as a synthetic target.

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Furthermore, the close structural relationship between narciclasine [(+)-**1**] and the generally more biologically active but much less abundant alkaloid pancratistatin [(+)-**3**] has prompted considerable effort to devise methods for converting the former compound into the latter.[11] The synthetic strategies used in accessing narciclasine [(+)-**1**] and its congeners have been the subject of a number of reviews including two recent and comprehensive ones.[1a,b] These reveal that a particularly successful approach has involved the construction of the C10a–C10b bond and the N5–C6 or C6–C6a bond using relevant aromatic and aminosugar or related fragments, including aminocyclitols, as building blocks.

Rigby and Mateo reported the first total synthesis of narciclasine in 1997.[12] This involved two key steps, namely the reaction of a 4-lithio-3-oxygenated-1,2-methylenedioxybenzene derivative with a polyoxygenated 1-cyclohexenylisocyanate to give, via C6–C6a bond formation, an adduct that could undergo a hydrogen bond-directed aryl enamide photocyclisation and thus establishing, via C10a–C10b bond formation, the full framework of the target alkaloid. Nine additional steps were then required to complete the synthesis. In 1999 Keck et al. described the next synthesis of (+)-**1**.[13] This employed a stereoselective 6-*exo*-radical cyclisation of an alkenyl radical to an *O*-benzyloxime radical acceptor group and thus generating the C4a–C10b bond of the final target. The alkenyl radical itself was generated by regioselective addition of the PhS• radical to a disubstituted alkyne that had been constructed via a Sonogashira reaction and accompanying establishment of the C10a–C10b bond. The radical cyclisation product then engaged in a straightforward lactam bond-forming reaction to create the N5–C6 bond of the target framework. Hudlicky and Gonzalez also reported a total synthesis of narciclasine in 1999.[14] In the early stages a brominated aminoconduritol derivative was constructed from an enantiopure *cis*-1,2-dihydrocatechol obtained through the whole-cell-mediated dihydroxylation of *o*-dibromobenzene. This derivative was then engaged in a Suzuki–Miyaura cross-coupling reaction with 3,4-methylenedioxy-5-methoxyphenyl boronic acid so as to produce, via a C10a–C10b bond-forming process, an arylated aminoconduritol. Various functional group interconversions followed to provide a derivative that was engaged in a modified Bischler–Napieralski reaction. This process delivered, via C6–C6a bond formation, a protected form of the target alkaloid. A two-step deprotection protocol, proceeding in 20% yield, then afforded narciclasine itself. The most recent synthesis of this natural product was reported, in 2002, by Elango and Yan.[15] Their approach has some parallels with the one Hudlicky used, in that an aminoconduritol building block was again employed although this was first epoxidised then N-alkylated with an *O*-protected form of 2-hydroxy-3,4-methylenedioxybenzyl bromide and so establishing the N5–C6 bond of the final target. Subjection of the product of this process to a $SnCl_4$-mediated and intramolecular Friedel–Crafts alkylation resulted in C10a–C10b bond formation and the establishment of the tetracyclic framework of the target alkaloid. Conventional FGIs were then applied to this material in completing the fourth total synthesis of narciclasine.

Our own, ongoing interests in developing new protocols for the preparation of various *Amaryllidaceae* alkaloids and their congeners via[16] coupled with the biological significance of narciclasine, prompted us to develop a synthesis of the title compound. Whilst the approach described below is amenable to the preparation of either enantiomeric form of narciclasine we deliberately targeted the unnatural form because this had not been prepared previously and, as a result, nothing is known about the biological profile of this material.

## 2. Results and discussion

Our recently reported syntheses of *ent*-lycoricidine [(−)-**2**] and various related compounds[16b] led us to consider the approach defined in Figure 1 as a means for obtaining *ent*-narciclasine [(−)-**1**]. In particular, a tandem Suzuki–Miyaura cross-coupling/amide bond forming process involving aryl boronate **4** and the aminoconduritol **6** would be expected to result in the formation of the C10a–C10b and N5–C6 bonds (no order implied) of the target compound and concomitant formation of the lactam ring of the target the framework. Exhaustive cleavage of the MOM-ether residues within the product expected of this process should then deliver the target compound (−)-**1**.

Whilst boronate **4** has not been reported previously, Keck has described the preparation of closely related systems[13] and so it was anticipated that this aromatic building block could be prepared from readily available piperonal (**5**) using directed *o*-metallation (DoM) protocols[17] to establish the relevant functionality on either side of the carbonyl unit within this starting material. The aminoconduritol building block **6**[16b] was employed in our recently reported synthesis of *ent*-lycoricidine and is generated, over nine rather conventional steps, from the *cis*-1,2-dihydrocatechol **7**. This last compound is readily available in large quantity and enantiomerically pure form through the whole-cell-mediated *cis*-1,2-dihydroxylation of bromobenzene (**8**) using a genetically engineered form of *Escherichia coli* that over-expresses the enzyme toluene dioxygenase (TDO) responsible for this fascinating biotransformation.[18] Compound **7** is available on a commercial basis from at least two sources.[19] Details associated with the syntheses of the aromatic and aminoconduritol cores, **4** and **6**, respectively, of *ent*-narciclasine are presented below in Parts 1 and 2.

### 2.1. Part 1: assembly of the aromatic core

The synthetic sequence employed in generating the aryl boronate **4** is shown in Scheme 1. This was based, in large part, on protocols introduced by Keck[13] for the purposes of generating the related aromatic synthon required in his synthesis of narciclasine. Thus, treatment of piperonal (**5**) with a mixture of sodium cyanide and manganese dioxide in neat diethylamine according to protocols defined by Gilman[20] resulted in the smooth formation of the diethylamide **9** (58% yield), which is presumably formed via a reaction sequence involving initial cyanohydrin formation then oxidation of this species to the corresponding α-ketonitrile that engages

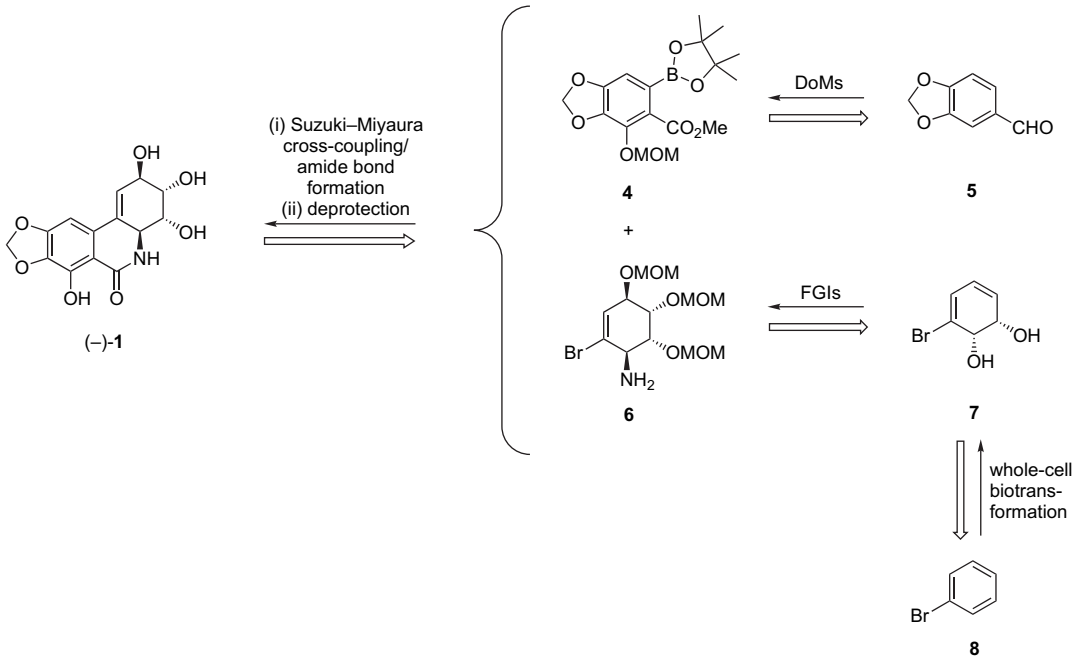
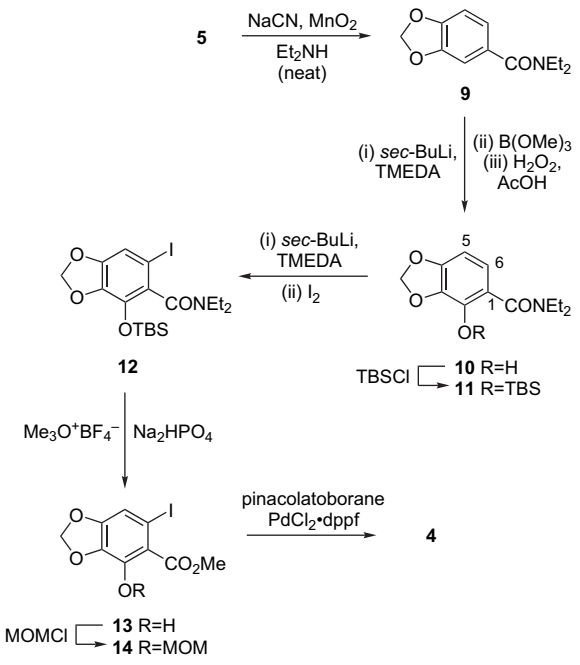



Figure 1.




Scheme 1.

in a nucleophilic addition/elimination sequence with diethylamine to give the observed product.

With the diethylcarboxamide moiety now installed as a directing group for *o*-metallation,[17] compound **9** was treated, successively, with *sec*-BuLi, trimethyl borate then hydrogen peroxide/acetic acid, so as to give, in a completely regio-controlled manner, the phenol **10** (90% yield).[21] The regiochemical outcome of this process is fully in accord with the DoM chemistry displayed by related compounds[17] and was readily confirmed through the observation of a 8.3 Hz coupling between H5 and H6 in the 300 MHz $^1$H NMR spectrum of phenol **10**. In anticipation of the next DoM event, the free hydroxyl group with this last compound was protected, using conventional conditions, as the corresponding TBS ether (**11**).[21] This was obtained in 94% yield after purification by flash chromatography. Subjection of compound **11** to reaction with *sec*-BuLi then molecular iodine afforded the requisite aryl iodide **12**[22] (90%) that was treated with trimethyloxonium tetrafluoroborate in the presence of dibasic sodium phosphate.[23] In this manner the diethylcarboxamide residue within compound **12** was methanolysed and the TBS-ether moiety cleaved so as to afford the methyl salicylate derivative **13**[13,23] in 62% yield. The structure of compound **13** follows from a single-crystal X-ray analysis, details of which are reported in Section 4. The derived ORTEP diagram is shown in Figure 2.

The free phenolic residue within this last compound was protected, under standard conditions, as the corresponding MOM ether **14** (99%) that was then subjected to a Miyaura borylation reaction[24] using pinacolatoborane in the presence of $PdCl_2 \cdot dppf$.

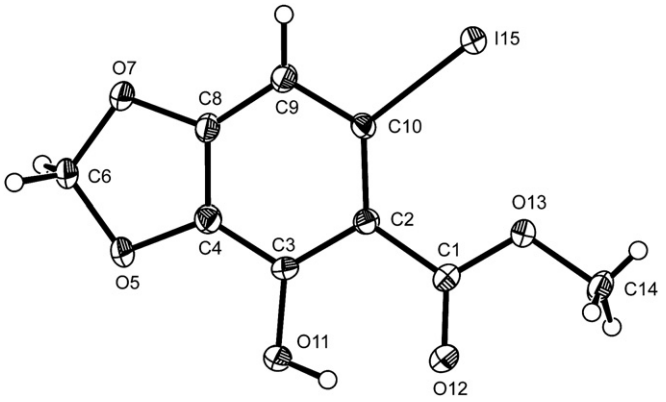



Figure 2. ORTEP diagram derived from the single-crystal X-ray analysis of compound **13**.

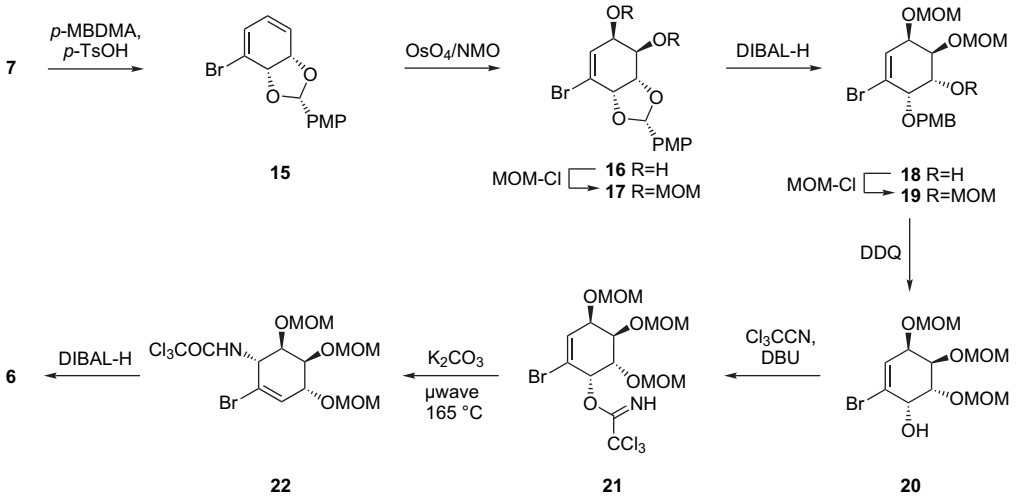
By such means the required aryl boronate **4** was obtained in 44% yield. Using a method recently described by Tønder et al.,[25] the yield of compound **4** could be raised to 54%. Inevitably this product was accompanied by varying amounts (14–22%) of the reductively de-iodinated material that has rather similar chromatographic properties to the desired compound **4**.

The spectral data derived from compound **4** were in complete accord with the assigned structure. In particular, the 75 MHz $^{13}C$ NMR spectrum displayed the expected 14 signals including 6 in the region above 105 ppm and attributable to $sp^2$-hybridised carbons within the compound. The 300 MHz $^1H$ NMR spectrum was dominated by a 12-proton singlet at $\delta$ 1.31 that clearly arises from the 4 equivalent methyl groups of the pinacolato residue. Distinct singlets were also observed for all the remaining proton environments within the compound. The 70 eV electron impact mass spectrum of this material showed a molecular ion at *m/z* 366 and an accurate mass measurement on this species established that it was of the expected composition, viz. $C_{17}H_{23}{}^{11}BO_8$.

Various attempts were made to shorten the reaction sequence shown in Scheme 1. In particular, and most obviously, the conversion of phenol **10** into the corresponding MOM ether rather than the illustrated TBS ether was investigated. While this conversion worked the subsequent methanolysis of the ensuing iodinated diethylcarboxamide did not. Similarly, while the anion derived from the reaction of compound **11** with *sec*-BuLi could be intercepted by various borylating agents the ensuing aryl boronate species failed to engage in Suzuki–Miyaura type cross-coupling reactions[26] with the aminoconduritol **6**.

### 2.2. Part 2: assembly of the aminoconduritol core

As noted above, the aminoconduritol **6** (Fig. 1) identified as the second key building block for the proposed synthesis of *ent*-narciclasine is a compound that we had prepared recently[16b] for the purposes of establishing a total synthesis of *ent*-lycoricidine. For the sake of completeness, however, a discussion of the reaction sequence (Scheme 2) used in generating compound **6** from metabolite **7** is provided here. This commences with the conversion, under conventional conditions, of *cis*-diol **7** into the corresponding *p*-methoxybenzylidene acetal **15**, which is obtained, predominantly, in the illustrated diastereoisomeric form. *cis*-1,2-Dihydroxylation of this last compound using the UpJohn conditions[27] proceeds with excellent levels of regio- and diastereo-control so as to give that product, **16** (65% from **7**), in which reaction has taken place at the more nucleophilic non-halogenated double bond and such that the hydroxyl groups are introduced onto the sterically less congested *exo*-face of the substrate. The hydroxyl groups within product **16** were each protected as the corresponding MOM ethers and the compound, **17** (ca. 75%), so-formed was subjected to reductive cleavage of the PMP-acetal moiety using DIBAL-H. In this manner the *tris*-ether **18** was obtained as the major product of reaction (84%). The regioselectivity observed in the conversion **17**→**18** is most likely the result of selective co-ordination of the DIBAL-H to that acetal oxygen within the former compound that is remote from the sterically demanding bromine. As a result the acetal C–O bond remote from the bromine is cleaved preferentially to give the observed benzyl ether **18** as the major product of reaction. Protection of the single free hydroxyl group within compound **18** as the corresponding MOM ether produced the fully protected conduritol **19** in 90% yield. The latter compound was treated with DDQ, which resulted in oxidative cleavage of the PMB-group and so affording the alcohol **20** in 95% yield. As a prelude to carrying out an Overman rearrangement,[28] compound **20** was treated with trichloroacetonitrile in the presence of DBU. The ensuing acetimidate **21** was then subject to heating under microwave irradiation (in the presence of potassium carbonate) and thereby undergoing the anticipated rearrangement to give the amide **22**, which was obtained in 78% yield from precursor **20**. To the best of our knowledge, the conversion **21**→**22** represents a rare example of a microwave-promoted Overman rearrangement[29] as well as the first example of such a process involving an halogenated alkene. Treatment of amide **22** with DIBAL-H then afforded the target aminoconduritol **6** in 89% yield. The spectral data recorded on this material were in full accord with the assigned structure but

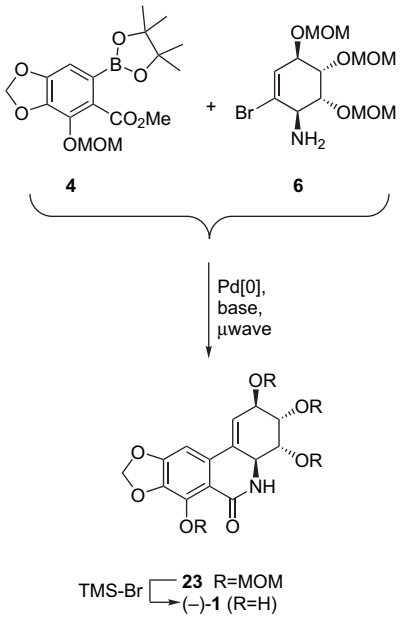



Scheme 2.

final confirmation of this came from its successful transformation into *ent*-lycoricidine[16b] and *ent*-narciclasine (vide infra).

### 2.3. Part 3: the endgame—coupling of the aromatic and aminoconduritol cores

With the two key building blocks, **4** and **6**, in hand the coupling of them so as to generate the narciclasine framework was pursued (Scheme 3). In the event, subjection of a toluene solution of a ca. 3:2 mixture of these materials to Suzuki–Miyaura cross-coupling under microwave conditions, using $Pd(PPh_3)_4$ as catalyst, aqueous $K_2CO_3$ as base and tetra-*n*-butylammonium bromide (TBAB) as phase-transfer catalyst, produced the anticipated tris-MOM ether, **23**, of *ent*-narciclasine in 63% yield after purification by flash chromatography. The ordering of events associated with this conversion remains unclear, viz. we do not know if the Suzuki–Miyaura cross-coupling reaction occurs before the amide bond-forming event or vice versa. In the final step of the synthetic sequence, compound **23** was subjected to reaction with ca. 30 molar equivalents of trimethylsilyl bromide, in dichloromethane at −40 to −10 °C for ca. 2.5 h, and thus affording *ent*-narciclasine [(−)-**1**] as a white crystalline solid in 48% yield.




Scheme 3.

The $^1H$ and $^{13}C$ NMR spectral data derived from *ent*-narciclasine proved essentially identical with those recorded for both the natural product[30,31] and synthetic samples of (+)-narciclasine produced by others[13] (Table 1). The specific rotation of *ent*-narciclasine {$[\alpha]_D$ −116 (*c* 0.21, methanol)} was of similar magnitude but opposite sign to that reported[13] for the naturally occurring enantiomer {$[\alpha]_D$ +112 (*c* 0.57, methanol)}.

The enantiomeric form, *ent*-**7**, of the *cis*-1,2-dihydrocatechol (**7**) used as the starting material in this synthesis is also available.[32] Accordingly, the work described here constitutes a formal total synthesis of the naturally occurring form of narciclasine.

## 3. Summary and conclusions

A comparison of the key features of all the reported syntheses of narciclasine, including the one detailed herein, is provided in Table 2. While the Hudlicky synthesis[14] and our own are the

Table 1
Comparison of the $^1H$ and $^{13}C$ NMR data recorded for synthetic [synth-**1**]- and naturally [nat-**1**]-derived samples of narciclasine with those arising from *ent*-narciclasine [(−)-**1**]

| $^{13}C$ NMR | | | $^1H$ NMR | | |
|---|---|---|---|---|---|
| synth-**1** ($\delta_C$)[a] | nat-**1** ($\delta_C$)[b] | (−)-**1** ($\delta_C$)[d] | synth-**1** ($\delta_H$)[e] | nat-**1** ($\delta_H$)[f] | (−)-**1** ($\delta_H$)[h] |
| 168.9 | 168.9 | 169.0 | 13.3 (s, 1H) | 13.24 (s, 1H) | 13.26 (s, 1H) |
| 152.4 | 152.3 | 152.4 | 7.91 (s, 1H) | 7.88 (s, 1H) | 7.92 (s, 1H) |
| 144.8 | 144.9 | 144.8 | 6.86 (s, 1H) | 6.84 (s, 1H) | 6.86 (s, 1H) |
| 133.4 | 133.4 | 133.5 | 6.15 (s, 1H) | 6.15 (ddd, 1H) | 6.15 (m, 1H) |
| 132.1 | 132.1 | 132.2 | 6.08 (d, 1H) | 6.09 (m, 2H)[g] | 6.09 (m, 2H) |
| 129.3 | 129.3 | 129.3 | 5.21–5.19 (m, 2H) | — | 5.20 (m, 2H, OH) |
| 124.8 | 124.6 | 124.8 | 5.04 (s, 1H) | — | 5.04 (d, 1H, OH) |
| 105.6 | 105.6 | 105.6 | 4.20 (d, 1H) | 4.18 (ddd, 1H) | 4.19 (d, 1H) |
| 102.1 | 102.8 | 102.2 | 4.01 (s, 1H) | 4.01 (ddd, 1H) | 4.01 (m, 1H) |
| 95.9 | 95.7 | 95.9 | 3.79 (d, 1H) | 3.78 (dd, 1H) | 3.78 (m, 1H) |
| 72.4 | 72.4 | 72.4 | 3.70 (s, 1H) | 3.69 (ddd, 1H) | 3.69 (m, 1H) |
| 69.2 | 69.2 | 69.2 | | | |
| 68.8 | 69.8[c] | 68.8 | | | |
| 52.9 | 52.8 | 52.9 | | | |

[a] Data from Ref. 13 and recorded in DMSO-$d_6$ at 125 MHz.
[b] Data from Ref. 30 and recorded in DMSO-$d_6$ at 22.5 MHz.
[c] We believe this chemical shift is in error and should be 68.8.
[d] Data arising from work reported in this paper and recorded in DMSO-$d_6$ at 125 MHz.
[e] Data from Ref. 13 and recorded in DMSO-$d_6$ at 500 MHz.
[f] Data from Ref. 31 and recorded in DMSO-$d_6$ at 500 MHz.
[g] In Ref. 31 this signal is actually identified as overlapping, one-proton doublets at $\delta$ 6.09 and 6.08 but has been presented as '6.09 (m, 2H)' in this table to facilitate comparisons with the other $^1H$ NMR data sets.
[h] Data arising from work reported in this paper and recorded in DMSO-$d_6$ at 500 MHz.

Table 2
Comparison of key features associated with the five reported syntheses of narciclasine or *ent*-narciclasine

| Lead author | Publication date | Key bond-forming sequence | Ring-forming sequence | Longest linear sequence | Overall yield (%) | Enantiomeric form produced |
|---|---|---|---|---|---|---|
| Rigby[12] | 1997 | C6–C6a then C10a–C10b | A+C→AC→ABC | 23 steps | 0.15 | (+) |
| Keck[13] | 1999 | C10a–C10b, C4a–C10b then N5–C6 | A→AC→ABC | 12 steps | 26 | (+) |
| Hudlicky[14] | 1999 | C10a–C10b then C6–C6a | C→AC→ABC | 11 steps | 0.7 | (+) |
| Tan[15] | 2002 | N5–C6 then C10a–C10b | C→AC→ABC | 15 steps | 16 | (+) |
| Present work | 2008 | C10a–C10b/N5–C6 | A+C→ABC | 11 steps | 7 | (−) |

shortest (eleven steps each), the Keck route[13] to (+)-narciclasine is only one step longer and stands out for its remarkable efficiency (26% overall yield). Tan's synthesis[15] is also notable for its rather high overall yield (16%), which is achieved over a fifteen-step sequence.

This study, when considered in conjunction with our earlier work,[16b,18b,33] serves to highlight the considerable utility of microbially-derived *cis*-1,2-dihydrocatechols such as **7** in the construction of a range of alkaloids and/or their analogues, including those of the lycorine-type. Indeed, current work in our laboratories is directed towards the total synthesis and biological evaluation of various other members of this rather significant 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 500 spectrometer, operating at 500 MHz for proton and 125 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 ($\delta$) [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 ($\delta$ 7.26), residual DMSO peak ($\delta$ 2.50) and the residual MeOH peak ($\delta$ 3.30) were used as references for $^1$H NMR spectra. The central peak ($\delta$ 77.0) of the $CDCl_3$ 'triplet' and the central peak ($\delta$ 39.5) of the DMSO-$d_6$ 'heptet' were used as references for proton-decoupled $^{13}$C NMR spectra. The data for $^{13}$C NMR spectra are given as: chemical shift ($\delta$), (protonicity), where protonicity is defined as: C=quaternary; CH=methine; $CH_2$=methylene; $CH_3$=methyl. Assignments of signals observed in various NMR spectra were often assisted by conducting Attached Proton Test (APT), homonuclear ($^1$H/$^1$H) correlation spectroscopy (COSY) and/or nuclear Overhauser effect (NOE) experiments. Infrared spectra ($\nu_{max}$) 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 $[\alpha]_D=100\times a/(c\times l)$ 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 (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). 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.[34] 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. Pinacolborane was purchased from Boron Molecular Ltd. (Melbourne, Australia). 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. N,N-Diethyl-1,3-benzodioxole-5-carboxamide (**9**)

Following a protocol reported by Gilman,[20] a magnetically stirred suspension of sodium cyanide (12.0 g, 245 mmol) in diethylamine (50 mL, 486 mmol), maintained under a nitrogen atmosphere at 0 °C, was treated with piperonal (9.00 g, 60 mmol), then $MnO_2$ (85 g, 977 mmol). The resulting mixture was warmed to 18 °C, stirred at this temperature for 48 h then filtered through Celite™ (4 cm deep pad contained

in a sintered-glass funnel). The solids thus retained were washed with $CH_2Cl_2$ (50 mL) and the combined filtrates concentrated under reduced pressure. The ensuing yellow oil was subjected to column chromatography (silica, 3:7→35:65→2:3 v/v ethyl acetate/hexane gradient elution) and concentration of the appropriate fractions ($R_f$=0.3 in 1:1 v/v ethyl acetate/hexane) afforded the title compound **9** (7.64 g, 58%) as a pale-tan crystalline solid, mp=66–69 °C (lit.[35] mp=64–66 °C). (Found: $M^{+\bullet}$, 221.1051. Calcd for $C_{12}H_{15}NO_3$ $M^{+\bullet}$, 221.1052.) $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.90–6.78 (complex m, 3H), 5.98 (s, 2H), 3.40 (br m, 4H), 1.17 (br m, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 170.6 (C), 148.2 (C), 147.4 (C), 130.8 (C), 120.4 (CH), 108.1 (CH), 107.3 (CH), 101.2 ($CH_2$), 43.2 (br, $CH_2$), 39.3 (br, $CH_2$), 14.1 (br, $CH_3$), 13.1 (br, $CH_3$); IR $\nu_{max}$ 2973, 2934, 1630, 1471, 1457, 1443, 1287, 1241, 1106, 1036, 917 cm$^{-1}$; MS *m/z* (EI, 70 eV) 221 ($M^{+\bullet}$, 58%), 220 (65), 149 (100), 121 (34), 91 (15), 65 (30).

#### 4.2.2. *N,N-Diethyl-4-hydroxy-1,3-benzodioxole-5-carboxamide (**10**)*

Compound **10** was prepared using a modification of a method described by Beak and Brown.[36] Thus, *sec*-BuLi (14.8 mL of a 1.4 M solution in cyclohexane, 20.7 mmol) was added to a magnetically stirred solution of TMEDA (3.1 mL, 20.7 mmol) in THF (130 mL) maintained under a nitrogen atmosphere at −78 °C. The resulting yellow solution was stirred at this temperature for 0.25 h then treated, via a cannula, with a solution of amide **9** (3.06 g, 13.83 mmol) in THF (70 mL) that had been precooled to −78 °C. The cannula was then flushed with additional THF (5 mL) to ensure that all of the substrate had been introduced into the reaction mixture. The ensuing tan solution was stirred at −78 °C for 2 h then treated, via a cannula, with a solution of trimethyl borate (3.1 mL, 27.7 mmol) in THF (50 mL) that had been precooled to −78 °C. The resulting mixture was stirred at 0 °C for 0.25 h, then warmed to 18 °C and stirred at this temperature for a further 2 h. After this time the reaction mixture was cooled to 0 °C and quenched with glacial acetic acid (2.8 mL, 48.9 mmol) then $H_2O_2$ (7.0 mL of 3:7 w/v aqueous solution). The ensuing mixture was stirred at 18 °C for 16 h, then partitioned between diethyl ether (100 mL) and $H_2O$ (100 mL). The separated aqueous phase was extracted with diethyl ether (3×100 mL) and the combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing residue was subjected to column chromatography (silica, 3:7 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate fractions ($R_f$=0.3 in 1:1 v/v ethyl acetate/hexane), the title compound **10**[21] (2.97 g, 90%) as a cloudy, white oil. (Found: $M^{+\bullet}$, 237.1000. Calcd for $C_{12}H_{15}NO_4$ $M^{+\bullet}$, 237.1001.) $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 10.09 (br s, 1H), 6.86 (d, $J$=8.3 Hz, 1H), 6.40 (d, $J$=8.3 Hz, 1H), 6.03 (s, 2H), 3.52 (q, $J$=7.2 Hz, 4H), 1.27 (t, $J$=7.2 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 171.0 (C), 150.6 (C), 143.4 (C), 135.2 (C), 121.5 (CH), 114.4 (C), 101.9 ($CH_2$), 99.7 (CH), 42.2 (2×$CH_2$), 13.3 (2×$CH_3$); IR $\nu_{max}$ 3200, 2976, 2937, 1634, 1592, 1463, 1310, 1288, 1062, 1032, 914 cm$^{-1}$; MS *m/z* (EI, 70 eV) 237 ($M^{+\bullet}$, 68%), 236 (40), 165 (100), 164 (85), 72 (58).

#### 4.2.3. *4-[[1,1-(Dimethylethyl)dimethylsilyl]oxy]-N,N-diethyl-1,3-benzodioxole-5-carboxamide (**11**)*

Imidazole (2.29 g, 33.7 mmol) and TBSCl (2.21 g, 14.6 mmol) were added to a magnetically stirred solution of alcohol **10** (2.67 g, 11.24 mmol) in $CH_2Cl_2$ (50 mL) maintained at 0 °C under an atmosphere of nitrogen. After 16 h at 18 °C the reaction mixture was diluted with brine (50 mL) and extracted with $CH_2Cl_2$ (4×50 mL). The combined organic extracts were then dried ($MgSO_4$), filtered and concentrated under reduced pressure to give a pale-yellow oil. Subjection of this material to flash chromatography (silica, 1:9→1:4 v/v ethyl acetate/hexane gradient elution) and concentration of the relevant fractions ($R_f$=0.3 in 3:7 v/v ethyl acetate/hexane) gave the title compound **11**[21] (3.70 g, 94%) as a clear, colourless oil, which solidified upon standing to give a white solid, mp=67–69 °C. [Found: $(M+H)^+$, 352.1937. Calcd for $C_{18}H_{29}NO_4Si$ $(M+H)^+$, 352.1944.] $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.68 (d, $J$=7.8 Hz, 1H), 6.50 (d, $J$=7.8 Hz, 1H), 5.94 (br s, 1H), 5.91 (br s, 1H), 3.51 (m, 2H), 3.19 (m, 2H), 1.22 (t, $J$=7.2 Hz, 3H), 1.01 (t, $J$=7.2 Hz, 3H), 0.94 (s, 9H), 0.21 (br s, 3H), 0.17 (br s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.3 (C), 148.8 (C), 136.7 (C), 135.2 (C), 125.4 (C), 120.6 (CH), 102.4 (CH), 100.8 ($CH_2$), 42.8 ($CH_2$), 39.3 ($CH_2$), 25.6 (3×$CH_3$), 18.1 (C), 13.9 ($CH_3$), 13.1 ($CH_3$), −4.5 ($CH_3$), −4.6 ($CH_3$); IR $\nu_{max}$ 2931, 1631, 1471, 1272, 1069, 1037, 840, 786 cm$^{-1}$; MS *m/z* (ESI) 374 [$(M+Na)^+$, 78%], 352 [$(M+H)^+$, 100], 279 (42).

#### 4.2.4. *4-[[1,1-(Dimethylethyl)dimethylsilyl]oxy]-N,N-diethyl-6-iodo-1,3-benzodioxole-5-carboxamide (**12**)*

Compound **12** was prepared using a modification of a method described by Keck et al.[13] Thus, *sec*-BuLi (9.2 mL of a 1.4 M solution in cyclohexane, 12.8 mmol) was added to a magnetically stirred solution of TMEDA (1.9 mL, 12.8 mmol) in THF (100 mL) maintained at −78 °C under a nitrogen atmosphere. The resulting yellow solution was stirred at this temperature for 0.25 h then cooled to −95 °C (MeOH/liquid $N_2$ bath) and treated, via cannula, with a solution of amide **11** (3.01 g, 8.56 mmol) in THF (50 mL) that had been precooled to −78 °C. The cannula was then flushed with additional THF (5 mL) to ensure that all of the substrates had been introduced into the reaction mixture. The ensuing tan solution was stirred at −95 °C for 1 h, then treated, via cannula, with a solution of iodine (4.35, 17.1 mmol) in THF (50 mL) that had been precooled to −78 °C. After the addition was complete, the reaction mixture was allowed to warm to 18 °C over 16 h and after this time it was concentrated under reduced pressure. The resulting dark-brown residue was dissolved in $CH_2Cl_2$ (300 mL) and the ensuing solution washed with $Na_2S_2O_5$ (3×50 mL of a saturated aqueous solution) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure. The ensuing yellow residue was subjected to column chromatography (silica, 1:9 v/v ethyl acetate/hexane elution) to afford, after concentration of the appropriate

fractions ($R_f$=0.4 in 1:4 v/v ethyl acetate/hexane), the title compound **12**[22] (3.70 g, 90%) as a clear, colourless oil. (Found: $M^{+\bullet}$, 477.0824. Calcd for $C_{18}H_{28}INO_4Si$ $M^{+\bullet}$, 477.0832.) $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.92 (d, $J$=0.6 Hz, 1H), 5.96 (dd, $J$=0.6 and 1.5 Hz, 1H), 5.92 (dd, $J$=1.5 and 0.6 Hz, 1H), 3.86 (m, 1H), 3.16 (m, 3H), 1.27 (t, $J$=7.2 Hz, 3H), 1.11 (t, $J$=7.2 Hz, 3H), 0.93 (s, 9H), 0.23 (s, 3H), 0.18 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.4 (C), 149.2 (C), 137.5 (C), 135.9 (C), 130.4 (C), 112.5 (CH), 101.3 ($CH_2$), 82.2 (C), 43.0 ($CH_2$), 39.2 ($CH_2$), 25.5 (3×$CH_3$), 18.2 (C), 13.8 ($CH_3$), 12.5 ($CH_3$), −4.2 ($CH_3$), −4.7 ($CH_3$); IR $\nu_{max}$ 2930, 1638, 1616, 1461, 1262, 1087, 1036, 862, 839, 786 cm$^{-1}$; MS *m/z* (EI, 70 eV) 477 ($M^{+\bullet}$, 1%), 462 (5), 421 (40), 420 (100), 405 (7), 292 (20), 264 (27), 73 (17).

### 4.2.5. Methyl 4-hydroxy-6-iodo-1,3-benzodioxole-5-carboxylate (*13*)

Compound **13** was prepared according to the method of Keck et al.[13] Thus, a magnetically stirred solution of compound **12** (4.22 g, 8.84 mmol) in $CH_3CN$ (45 mL) maintained under an atmosphere of nitrogen was treated with $Na_2HPO_4$ (1.88 g, 13.26 mmol), then $Me_3OBF_4$ (3.92 g, 26.52 mmol). The ensuing mixture was stirred at 18 °C for 5 h before being quenched with $NaHCO_3$ (55 mL of a saturated aqueous solution then 4 g of solid material). The resulting mixture was stirred at 18 °C for 16 h, then diluted with $CH_2Cl_2$ (100 mL) and stirred at 18 °C for a further 2 h. The separated aqueous phase was extracted with $CH_2Cl_2$ (3×100 mL) and the combined organic phases were then dried ($Na_2SO_4$), filtered and concentrated under reduced pressure. The ensuing pale-yellow solid was subjected to column chromatography (silica, 2:3 v/v hexane/$CH_2Cl_2$) to afford, after concentration of the appropriate fractions ($R_f$=0.4 in 3:7 v/v hexane/$CH_2Cl_2$), the title compound **13**[13] (1.78 g, 62%) as a colourless, crystalline solid, mp=165–166 °C (lit.[13] mp=154–155 °C). (Found: $M^{+\bullet}$, 321.9338. Calcd for $C_9H_7IO_5$ $M^{+\bullet}$, 321.9338.) $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 11.03 (s, 1H), 7.20 (s, 1H), 6.08 (s, 2H), 3.96 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.7 (C), 152.6 (C), 146.8 (C), 135.6 (C), 115.4 (CH), 112.3 (C), 102.9 ($CH_2$), 84.6 (C), 51.9 ($CH_3$); IR $\nu_{max}$ 3436, 2920, 1666, 1434, 1301, 1081, 1037, 786 cm$^{-1}$; MS *m/z* (EI, 70 eV) 322 ($M^{+\bullet}$, 43%), 290 (100), 105 (25).

### 4.2.6. Methyl 6-iodo-4-(methoxymethoxy)-1,3-benzodioxole-5-carboxylate (*14*)

A magnetically stirred solution of phenol **13** (1.78 g, 5.53 mmol) in THF (60 mL) maintained at 0 °C under a nitrogen atmosphere was treated with NaH (290 mg of a ca. 60% dispersion in mineral oil, 7.19 mmol) and the resulting mixture was allowed to warm to 18 °C. After 0.25 h the reaction mixture was cooled to 0 °C then treated, dropwise, with MOMCl (550 μL, 7.19 mmol). The ensuing mixture was stirred at 18 °C for a further 16 h then diluted with diethyl ether (50 mL), poured into water (50 mL) and the separated aqueous phase was extracted with diethyl ether (4×50 mL). The combined organic fractions were dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a pale-yellow oil. Subjection of this material to column chromatography (silica, 1:4 v/v ethyl acetate/hexane elution) provided, after concentration of the appropriate fractions ($R_f$=0.3 in 3:7 v/v ethyl acetate/hexane), the *title compound* ***14*** (2.02 g, 99%) as a clear, colourless oil. (Found: $M^{+\bullet}$, 365.9607. $C_{11}H_{11}IO_6$ requires $M^{+\bullet}$, 365.9600.) $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.98 (s, 1H), 5.98 (s, 2H), 5.24 (s, 2H), 3.92 (s, 3H), 3.48 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 167.3 (C), 150.6 (C), 137.4 (C), 137.2 (C), 128.0 (C), 113.6 (CH), 102.0 ($CH_2$), 96.7 ($CH_2$), 81.1 (C), 57.1 ($CH_3$), 52.8 ($CH_3$); IR $\nu_{max}$ 1732, 1615, 1464, 1258, 1055, 1031, 927 cm$^{-1}$; MS *m/z* (EI, 70 eV) 366 ($M^{+\bullet}$, 61%), 335 (20), 305 (21), 290 (100), 45 (85).

### 4.2.7. Methyl 4-(methoxymethoxy)-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-1,3-benzodioxole-5-carboxylate (*4*)

*Method A*: A magnetically stirred solution of iodide **14** (157 mg, 0.43 mmol) in $CH_3CN$ (2 mL) was treated with $Et_3N$ (180 μL, 1.29 mmol) and $PdCl_2$·dppf (35 mg, 0.04 mmol) then, dropwise, with pinacolborane (125 μL, 0.86 mmol). The ensuing red solution was heated at 100 °C in a CEM Explorer™ microwave reactor for 0.5 h then cooled to 18 °C and diluted with diethyl ether (30 mL). The ensuing mixture was poured into brine (10 mL) and the separated aqueous layer extracted with diethyl ether (3×20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The resulting dark-brown oil was subjected to column chromatography (silica, 1:9→15:85 v/v ethyl acetate/hexane gradient elution) to provide two fractions, A and B.

Concentration of fraction A [$R_f$=0.3(1) in 3:7 v/v ethyl acetate/hexane] afforded *methyl 4-(methoxymethoxy)-1,3-benzodioxole-5-carboxylate* (14 mg, 14%) as a clear, colourless oil. (Found: $M^{+\bullet}$, 240.0634. $C_{11}H_{12}O_6$ requires $M^{+\bullet}$, 240.0634.) $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 7.48 (d, $J$=8.4 Hz, 1H), 6.61 (d, $J$=8.4 Hz, 1H), 6.03 (s, 2H), 5.28 (s, 2H), 3.86 (s, 3H), 3.57 (s, 3H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 165.7 (C), 152.3 (C), 140.4 (C), 139.0 (C), 126.5 (CH), 118.2 (C), 103.6 (CH), 101.9 ($CH_2$), 97.9 ($CH_2$), 57.1 ($CH_3$), 51.9 ($CH_3$); IR $\nu_{max}$ 1723, 1624, 1601, 1466, 1274, 1157, 1055, 1033, 929 cm$^{-1}$; MS *m/z* (EI, 70 eV) 240 ($M^{+\bullet}$, 40%), 209 (23), 179 (26), 164 (89), 45 (100).

Concentration of fraction B [$R_f$=0.2(9) in 3:7 v/v ethyl acetate/hexane] afforded the *title compound* ***4*** (69 mg, 44%) as a clear, pale-tan coloured oil. (Found: $M^{+\bullet}$, 366.1481. $C^{17}H_{23}{}^{11}BO_8$ requires $M^{+\bullet}$, 366.1486.) $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ 6.92 (s, 1H), 6.00 (s, 2H), 5.25 (s, 2H), 3.87 (s, 3H), 3.51 (s, 3H), 1.31 (s, 12H); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ 168.7 (C), 150.3 (C), 139.8 (C), 137.5 (C), 127.3 (C), 109.3 (CH), 102.0 ($CH_2$), 97.4 ($CH_2$), 84.3 (2×C), 57.3 ($CH_3$), 52.7 ($CH_3$), 25.0 (4×$CH_3$) (one signal obscured or overlapping); IR $\nu_{max}$ 2978, 1736, 1607, 1419, 1382, 1259, 1143, 1055, 1035, 971, 847 cm$^{-1}$; MS *m/z* (EI, 70 eV) 366 ($M^{+\bullet}$, 7%), 335 (13), 308 (100), 290 (23), 235 (37), 208 (41), 190 (27), 83 (23), 45 (53).

*Method B*: A procedure described by Tønder et al. was employed.[25] Thus, a magnetically stirred solution of iodide **14** (246 mg, 0.67 mmol) in 1,4-dioxane (2 mL) was treated with $Et_3N$ (370 μL, 2.69 mmol) then $Pd(OAc)_2$ (8 mg, 0.03 mmol) and 2-(dicyclohexylphosphino)biphenyl (47 mg, 0.13 mmol). The resulting orange-coloured mixture was heated to 80 °C then treated, dropwise, with pinacolborane (295 μL, 2.02 mmol). Heating at 80 °C was continued for 1.33 h then the reaction mixture was cooled to 18 °C and treated, dropwise, with $H_2O$ (300 μL) before being diluted with $CH_2Cl_2$ (50 mL) and additional $H_2O$ (10 mL). The separated aqueous layer was extracted with $CH_2Cl_2$ (2×50 mL) and the combined organic phases were dried ($Na_2SO_4$) then filtered and concentrated under reduced pressure. The resulting dark-brown oil was subjected to column chromatography (silica, 1:9→15:85 v/v ethyl acetate/hexane gradient elution) to provide two fractions, A and B.

Concentration of fraction A [$R_f$=0.3(1) in 3:7 v/v ethyl acetate/hexane] afforded methyl 4-(methoxymethoxy)-1,3-benzodioxole-5-carboxylate (35 mg, 22%) as a clear, brown oil. This material was identical, in all respects, to fraction A obtained using Method A as detailed immediately above.

Concentration of fraction B [$R_f$=0.2(9) in 3:7 v/v ethyl acetate/hexane] afforded the title compound **4** (134 mg, 54%) as a clear, brown oil. This material was identical, in all respects, to fraction B obtained using Method A as detailed immediately above.

#### *4.2.8. (1R,4R,5S,6R)-2-Bromo-4,5,6-tris(methoxymethoxy)-cyclohex-2-enamine (**6**)*

Aminoconduritol **6** was prepared, over nine steps, from commercially available *cis*-1,2-dihydrocatechol **7** employing protocols we have described previously[16b] save for the use of freshly distilled DBU in the conversion **20**→**21**, which allowed the yield for this step to be raised from 65% to 78%.

#### *4.2.9. (2R,4R,3S,4aS)-2,3,4,7-Tetra(methoxymethoxy)-2,3,4,5,4a-pentahydro-9H-1,3-dioxoleno[4,5-j]phenanthridin-6-one (**23**)*

A magnetically stirred mixture of amine **6** (42 mg, 0.12 mmol) in toluene (1.5 mL) and $H_2O$ (1.5 mL) was treated with boronate ester **4** (68 mg, 0.19 mmol), $K_2CO_3$ (50 mg, 0.35 mmol), TBAB (10 mg, 0.03 mmol) and $Pd(PPh_3)_4$ (20 mg, 0.02 mmol). The ensuing mixture was stirred at 120 °C in a CEM Explorer™ microwave reactor for 0.5 h then cooled, diluted with $CH_2Cl_2$ (50 mL) and washed with $H_2O$ (1×10 mL) before being dried ($MgSO_4$), filtered and concentrated under reduced pressure to afford a dark-brown oil. Subjection of this material to column chromatography (silica, 1:99→1.5:98.5 v/v MeOH/$CH_2Cl_2$ gradient elution) provided, after concentration of the appropriate fractions ($R_f$=0.4 in 5:95 v/v MeOH/$CH_2Cl_2$), the *title compound* ***23*** (50 mg including 14 mg of triphenylphosphine oxide, 63% of **23**) as a yellow foam. (Found: $M^{+\bullet}$, 483.1740. $C_{22}H_{29}NO_{11}$ requires $M^{+\bullet}$, 483.1741.) $^1$H NMR ($CDCl_3$, 300 MHz) δ 6.80 (s, 1H), 6.39 (br s, 1H, NH), 6.06 (br m, 1H), 6.05 (d, *J*=1.5 Hz, 1H), 6.02 (d, *J*=1.5 Hz, 1H), 5.28 (m, 2H), 4.86–4.67 (complex m, 6H), 4.43 (m, 1H), 4.29 (m, 1H), 4.14 (m, 1H), 3.93 (dd, *J*=2.1 and 8.7 Hz, 1H), 3.60 (s, 3H), 3.50 (s, 3H), 3.38 (s, 3H), 3.37 (s, 3H); MS *m/z* (EI, 70 eV) 483 ($M^{+\bullet}$, 6%), 439 (9), 291 (13), 45 (100).

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

#### *4.2.10. (2R,4R,3S,4aS)-2,3,4,7-Tetrahydroxy-2,3,4,5,4a-pentahydro-9H-1,3-dioxoleno[4,5-j]phenanthridin-6-one [ent-narciclasine] [(−)-**1**]*

A magnetically stirred solution of compound **23** (50 mg including 14 mg of triphenylphosphine oxide, 0.074 mmol of **23**) in $CH_2Cl_2$ (2 mL) maintained under a nitrogen atmosphere at −40 °C was treated with TMSBr (270 μL, 2.09 mmol). The resulting mixture was warmed to −20 °C over ca. 0.5 h, stirred at −20 to −10 °C for 2 h then treated with $NaHCO_3$ (2 mL of a saturated aqueous solution then 176 mg of solid material). The ensuing mixture was warmed to 18 °C, stirred at this temperature for 0.5 h, then treated with TLC-grade silica (ca. 1 g). The solvents were removed under reduced pressure, and the resulting white powder loaded onto a 5 cm×1.5 cm column of TLC-grade silica that was then eluted with $CH_2Cl_2$ followed by 2:98→4:96→5:95→1:9 v/v MeOH/$CH_2Cl_2$. Concentration of the appropriate fractions ($R_f$=0.4 in 1:4 v/v MeOH/$CH_2Cl_2$) afforded the *title compound (−)-**1*** (11 mg, 48%) as a white, crystalline solid, mp >250 °C with discolouration commencing at 180 °C, $[\alpha]_D$ −116 (*c* 0.21, MeOH) [lit.[13] (for narciclasine) $[\alpha]_D$ +112 (*c* 0.57, MeOH)]. [Found: $(M+Na)^+$, 330.0599 and $(M+H)^+$, 308.0768. $C_{14}H_{13}NO_7$ requires $(M+Na)^+$, 330.0590 and $(M+H)^+$, 308.0770.] $^1$H NMR (500 MHz, $CD_3OD$) δ 6.76 (s, 1H), 6.16 (m, 1H), 6.03 (m, 2H), 4.34 (m, 1H), 4.22 (m, 1H), 3.89 (m, 2H); $^1$H NMR (500 MHz, DMSO-$d_6$), see Table 1; $^{13}$C NMR (75 MHz, DMSO-$d_6$), see Table 1; IR $\nu_{max}$ 3429, 2918, 1676, 1472, 1379, 1262, 1231, 1089, 1031 $cm^{-1}$; MS *m/z* (ESI) 330 [$(M+Na)^+$, 100%], 308 [$(M+H)^+$, 95].

### *4.3. Crystallographic study on compound **13***

#### *4.3.1. Crystal data*

$C_9H_7IO_5$, $M$=322.06, $T$=200(1) K, orthorhombic, space group $P2_12_12_1$, $Z$=4, $a$=4.1771(2), $b$=6.9480(3), $c$=33.0128(15) Å, $V$=958.11(7) Å$^3$, $D_x$=2.233 g cm$^{-3}$, 2147 unique data ($2\theta_{max}$=55°), 1877 with $I>3.0\sigma(I)$; $R$=0.030, $Rw$=0.034, $S$=1.12.

#### *4.3.2. Structure determination*

Images were measured on a Nonius Kappa CCD diffractometer (Mo Kα, graphite monochromator, λ=0.71073 Å) and data extracted using the DENZO package.[37] Structure solution was by direct methods (SIR92).[38] The structure of compound **13** was refined using the CRYSTALS program package.[39] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC no. 662224). These data can be obtained free-of-charge via www.ccdc.cam.ac.uk/data_request/cif, by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic

Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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