CSIRO PUBLISHING

RESEARCH FRONT

Aust. J. Chem. **2015**, *68*, 241–247
http://dx.doi.org/10.1071/CH14520

Full Paper

A Chemoenzymatic Route to the (+)-Form of the Amaryllidaceae Alkaloid Narseronine*

Shuxin Yang,[A] *Martin G. Banwell,*[A,B] *Anthony C. Willis,*[A] *and Jas S. Ward*[A]

[A]Research School of Chemistry, Institute of Advanced Studies, The Australian National University, Canberra, ACT 2601, Australia.
[B]Corresponding author. Email: martin.banwell@anu.edu.au

The enzymatically derived and enantiopure *cis*-1,2-dihydrocatechol **1** has been converted, over 14 one-pot operations, into the (+)-form of the alkaloid narseronine (**2**). The present study, which complements earlier work that established a route from metabolite **1** to enantiomer (−)-**2**, involves an *N*-bromosuccinimide/tri-*n*-butyltin hydride-mediated cyclisation reaction to construct the unsaturated B-ring lactone of the target compound.

Manuscript received: 26 August 2014.
Manuscript accepted: 7 September 2014.
Published online: 3 November 2014.

Introduction

cis-1,2-Dihydrocatechols such as **1** are readily obtained in enantiomerically pure form (viz. >99.8 % ee) through the whole-cell biotransformation of the corresponding arene (bromobenzene in this case) using mutant forms of bacteria that produce toluene dioxygenase (TDO), the enzyme responsible for this fascinating conversion.[1,2] Metabolites such as **1** have proved to be particularly effective starting materials for the chemical synthesis of a remarkably diverse range of chiral, non-racemic natural products and/or biologically active compounds.[2] However, an ongoing issue associated with this (chemoenzymatic[3]) approach to the construction of such target systems is the seeming confinement of it to the generation of a single enantiomeric form of a given target molecule.[4] As part of an effort to address such constraints, Hudlicky and his coworkers demonstrated that the 'latent' symmetry elements associated with compound **1** and certain of its congeners[2a,d] allow their use in the enantiodivergent synthesis of, inter alia, cyclitols.[5] Similarly, we have shown that various *cis*-1,2-dihydrocatechols can participate in a range of Diels–Alder cycloaddition processes that permit the assembly of either enantiomeric form of certain polycyclic frameworks, including those associated with sesquiterpenoid natural products.[6] In a related vein, we now detail the outcomes of a study that has culminated in the identification of a method for the assembly of the (+)-form of the Amaryllidaceae alkaloid narseronine (**2**)[7] from compound **1**, work that complements our recently reported synthesis[8] of its optical antipode [viz. (−)-narseronine] from the same starting material (Chart 1).

The key features of our previously reported synthesis of (−)-narseronine [(−)-**2**] involved the initial conversion (Scheme 1) of metabolite **1** into the well-known derivative **3** (95 %),[5] which was itself engaged in selective epoxide ring-opening on treatment with the anion derived from acetonitrile.

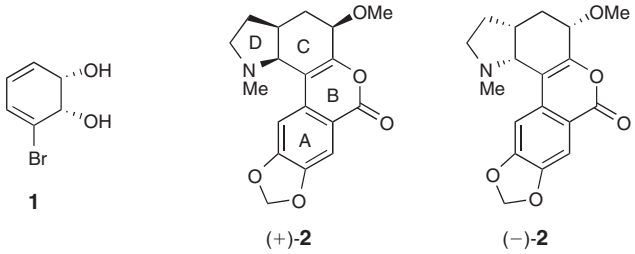


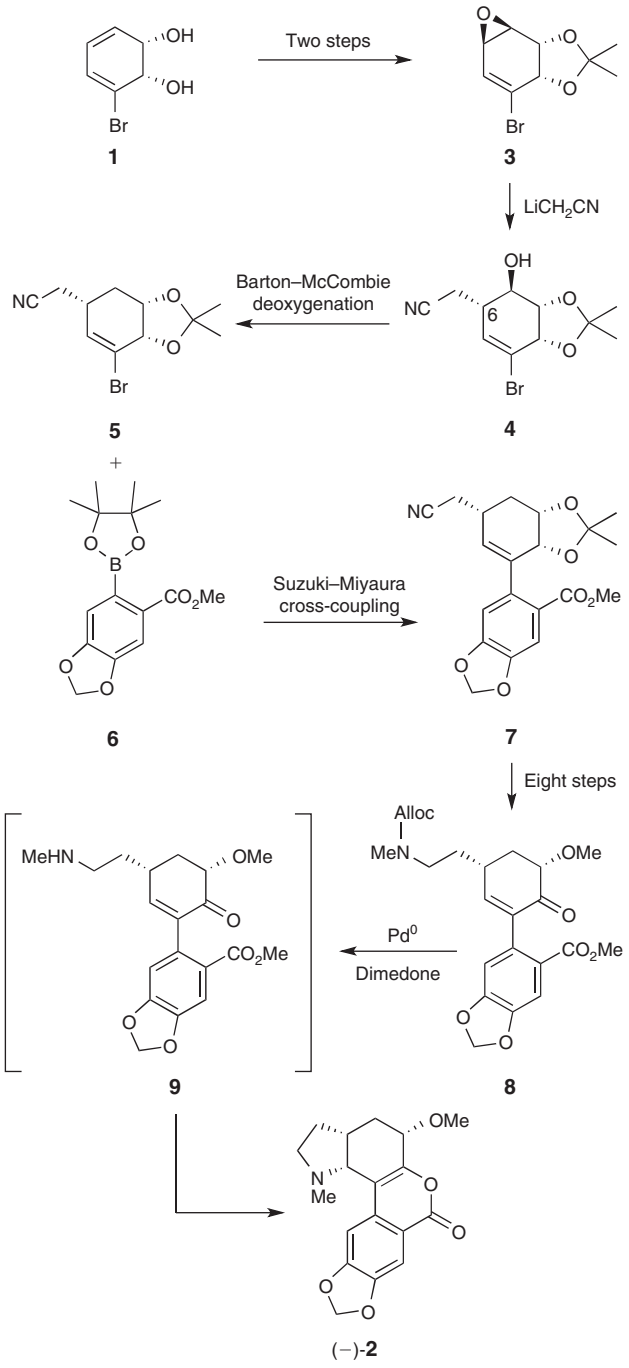
Chart 1.

The product alcohol **4** (96 %)[9] was then deoxygenated using the Barton–McCombie protocol[10] so as to afford the bromoalkene **5** (82 %) that participates in a Suzuki–Miyaura cross-coupling reaction with the arylboronate **6**[9] to give compound **7** (75 %). Various manipulations of this last compound including the Raney-cobalt mediated reduction of the associated nitrile residue[9,11] afforded, over eight steps and in 16 % overall yield, the α-arylated cyclohexenone **8** carrying a protected secondary amine residue tethered through the γ-carbon. Finally, treatment of compound **8** with $(Ph_3P)_4Pd$ in the presence of dimedone resulted in cleavage of the Alloc group, thus allowing the resulting secondary amine **9** (which was not isolated) to undergo an intramolecular hetero-Michael addition reaction/*trans*-acylation sequence and so affording (−)-narseronine [(−)-**1**] (82 %), the structure of which was secured by single-crystal X-ray analysis. Unfortunately, the specific rotation for the natural product obtained by Bastida et al.[7] was not reported and so it has not been possible to establish its absolute configuration.

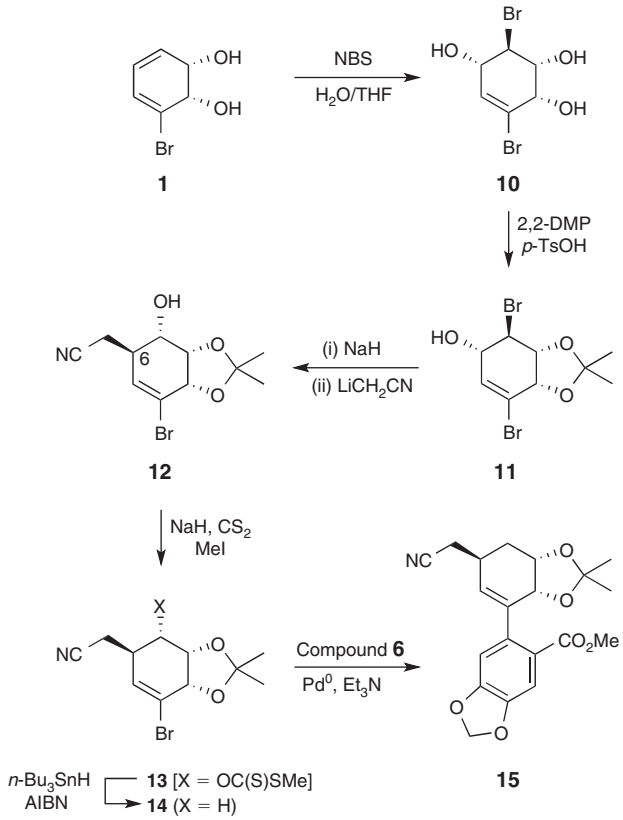
Results and Discussion

The synthetic route used to effect the conversion **1** → (+)-**2**, the focus of the study reported herein, relied, in its early

*Dedicated to Des Brown in recognition of his seminal and sustained contributions to the chemistry of heterocyclic compounds.



Scheme 1.

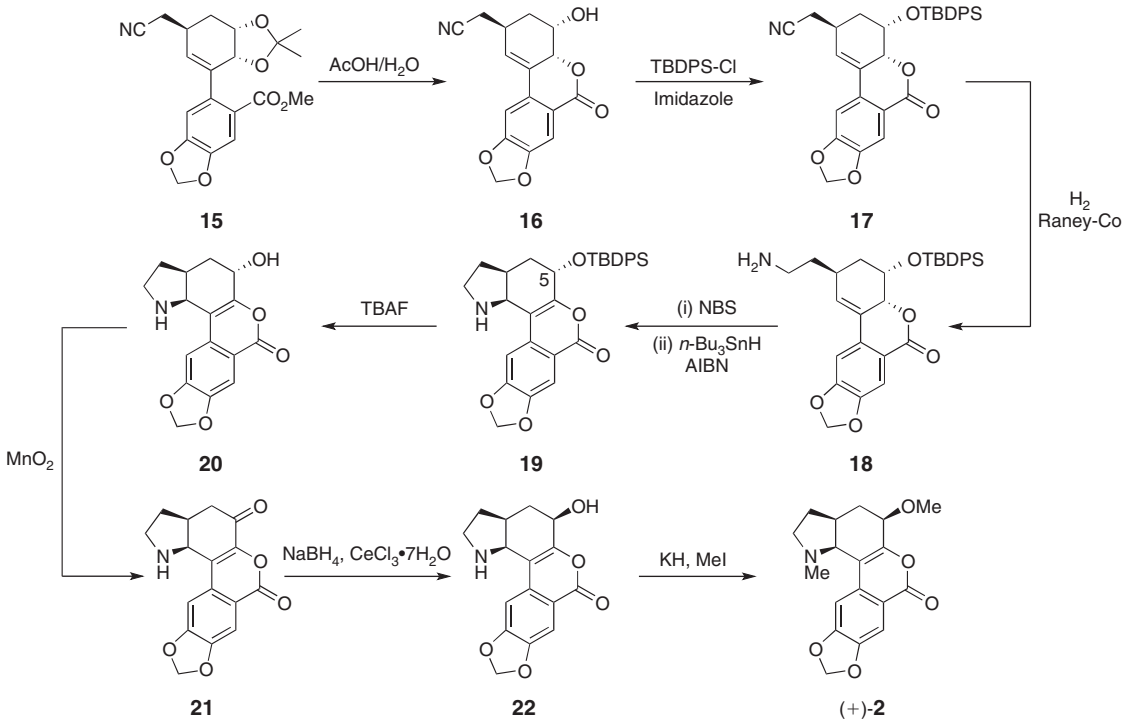


Scheme 2.

stages (Scheme 2), on chemistry established during the course of preparing the non-natural enantiomeric form of the alkaloid clividine.[12] Specifically, diene **1** was treated with *N*-bromosuccinimide (NBS) in wet THF, thus generating, in a completely regio- and diastereo-selective manner, bromohydrin **10**[12] that was readily protected as the corresponding acetonide **11**[12] (92 % from **1**) under conventional conditions. Successive treatment of compound **11** with sodium hydride (so as to form the corresponding epoxide) and then the anion of acetonitrile (which was generated in situ by treating acetonitrile itself with *n*-BuLi) afforded the previously reported[12] γ-hydroxynitrile **12** (87 %). Conversion of compound **12** into the corresponding methyl xanthate **13**[12] (93 %) was achieved under conventional conditions and this was then subjected to a Barton–McCombie deoxygenation reaction using tri-*n*-butyltin hydride and 2,2′-azobis(2-methylpropionitrile) (AIBN) in refluxing benzene and thus generating the deoxygenated congener of alcohol **12**, viz. compound **14**.[12] This was obtained in 87 % yield. Suzuki–Miyaura cross-coupling of bromoalkene **14** with the arylboronate **6**[9] proceeded smoothly on using $PdCl_2(dppf)\cdot CH_2Cl_2$ in the presence of triethylamine and thereby providing the previously reported compound **15**[12] in 95 % yield.

The chemistry used to complete the synthesis of (+)-narseronine [(+)-**2**] is shown in Scheme 3 and began with the exposure of the Suzuki–Miyaura cross-coupling product **15** to aqueous acetic acid at 50°C such that the allylic hydroxyl group of the initially formed diol reacted with the proximate ester residue to afford the lactone **16** (84 %).[12] The free hydroxyl group within this last compound was protected as the corresponding TBDPS-ether **17**[12] (80 %) using conventional protocols and this was, in turn, subjected to reaction with dihydrogen in the presence of Raney-cobalt[13] in ammoniacal methanol to produce the previously reported primary amine **18** (82 %).[12] In a pivotal step of the reaction sequence, this last compound was treated successively with 1.1 molar equivalents of NBS, then, after 0.5 h, with tri-*n*-butyltin hydride (*n*-Bu_3SnH) and AIBN, so affording compound **19** (83 %), which now incorporates the unsaturated B-ring lactone and, therefore, the full polycyclic framework of (+)-narseronine [(+)-**2**].

The exact pathway followed during the conversion **18** → **19** remains unclear at the present time but it seems likely that the initial step involves the formation of the *N*-bromo-derivative of the former compound (through halogen atom transfer from NBS) and that this derivative reacts with *n*-Bu_3SnH to give the corresponding nitrogen-centred radical, which itself engages in a 5-exo-trig cyclisation process to give the tetracyclic benzylic



Scheme 3.

radical. The precise means by which this last species is converted into the final, alkene-containing product remains to be determined but it is conceivable that another bromine atom transfer is involved, thus forming a benzylic bromide that promptly loses the elements of HBr and thereby generating compound **19**.

Completion of the synthesis of (+)-narseronine [(+)-**2**] from compound **19** required inversion of configuration at C5 as well as *N*- and *O*-methylation reactions. The best means of addressing the first of these requirements was to cleave the TBDPS ether residue within the latter compound using tetra-*n*-butylammonium fluoride (TBAF) and then oxidising the resulting alcohol **20** (95 %) with MnO_2 and so forming the ketone **21** (78 %). All the ^{1}H and ^{13}C NMR spectral data acquired on products **20** and **21** were in complete accord with the assigned structures but final confirmation of these followed from a single-crystal X-ray analysis on the former compound. The derived *ORTEP* is shown in Fig. 1 and various crystal data are presented in the Experimental section. Treatment of compound **21** with the Luche reagent[14] derived from reacting sodium borohydride and $CeCl_3$ heptahydrate in methanol resulted in the essentially exclusive formation of the C5 epimer of compound **20**, namely alcohol **22**, which was obtained in 99 % yield and the structure of which was also secured by single-crystal X-ray analysis. Presumably, the stereochemical outcome of this 1,2-reduction process derives from the steric impositions of the β-orientated pyrrolidine ring that ensure hydride is delivered to the α-face of the ketone carbonyl unit.

The necessary *N*,*O*-dimethylation of aminoalcohol **22** so as to generate (+)-narseronine proved to be a remarkably difficult transformation. So, for example, treatment of the former compound with methyl iodide and silver(I) oxide (no solvent) afforded a complex mixture of products from which a small amount of a rather unstable crystalline compound could be obtained. A single-crystal X-ray analysis of this material

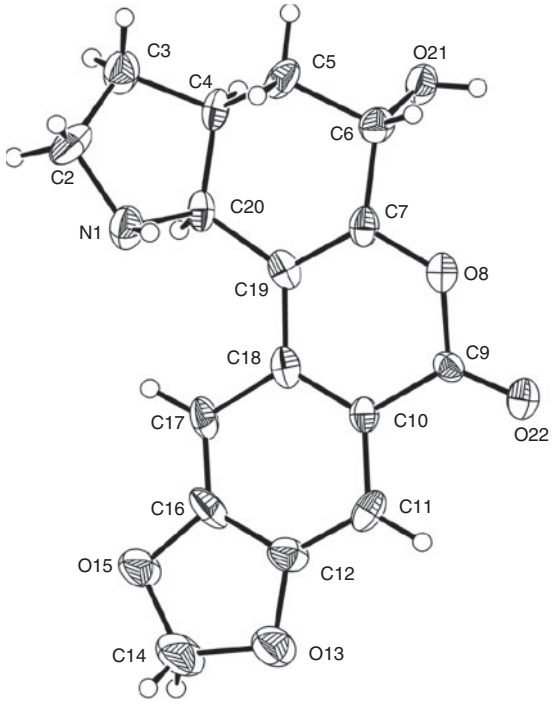
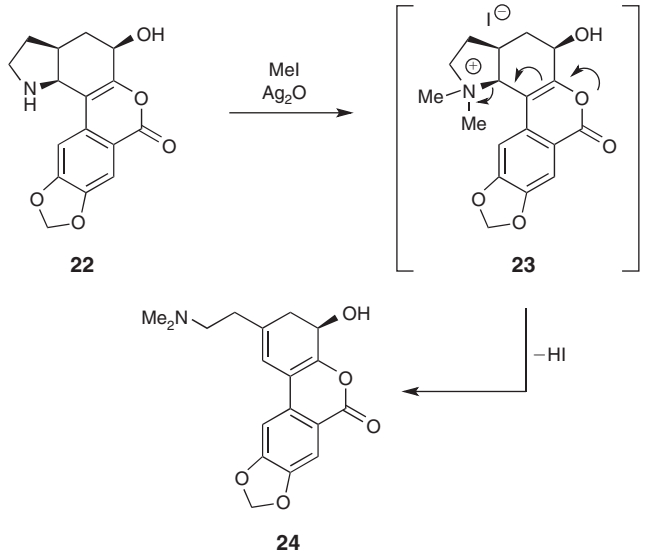


Fig. 1. *ORTEP* derived from the single-crystal X-ray analysis of compound **20** (CCDC no. 944982) with labelling of selected atoms. Anisotropic displacement ellipsoids display 30 % probability levels. Hydrogen atoms are drawn as circles with small radii.

established that it was the arene hydrate **24** (Scheme 4).[15] This presumably arises via a two-fold *N*-methylation of substrate **22** to produce the methiodide salt **23** which itself fragments in the illustrated manner to give, after loss of the elements of hydrogen iodide, the observed product. Eventually, it was established that



Scheme 4.

when a THF solution of compound **22** maintained at 0–18°C was treated with ~4 molar equivalents of potassium hydride and 8 equivalents of methyl iodide (Scheme 3), then a relatively clean *N*,*O*-bismethylation reaction took place and thus finally providing (+)-narseronine [(+)-**2**] in 83 % yield after chromatographic purification. The ^{1}H and ^{13}C NMR spectral data obtained on this material matched those recorded earlier[8] for its enantiomer but final confirmation of its structure (other than absolute stereochemistry) followed from a single-crystal X-ray analysis. The specific rotation of compound (+)-**2** was +21.0 (*c* 0.3, $CDCl_3$). This compares with the value of −25.4 (*c* 1.6, $CDCl_3$) recorded[8] for its enantiomer.

Conclusions

The ability to effect syntheses of both (+)- and (−)-narseronine [(+)-**2** and (−)-**2**, respectively] from the *cis*-1,2-dihydrocatechol **1** serves to further emphasise the utility of such systems as starting materials in chemical synthesis. In this instance, the capacity for enantiodivergence arises by virtue of being able to readily generate the isomeric nitriles **4** and **12**, the C6 stereochemistries of which determine the orientations (α or β) of the derived pyrrolidine or D-rings in the product enantiomers (−)-**2** and (+)-**2**, respectively. In the case of the reaction sequence leading to the latter form of the title alkaloid, an inversion of configuration at C5 in compound **19** is required. Despite this, the lengths of the two reaction sequences are similar (viz. 14 vs 15 steps), not least because of the more efficient means of introducing the methyl group at nitrogen in the one reported here. Extensions of the chemistries defined above to the assembly of both enantiomeric forms of related alkaloids are now being pursued. Results will be reported in due course.

Experimental

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 spectrometer operating at 400 MHz for proton and 100 MHz for carbon nuclei. ^{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 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. Infrared spectra (ν_{max}) were recorded on a Perkin–Elmer 1800 Series Fourier-transform (FT)IR spectrometer. Samples were analysed as thin films on KBr plates. Low-resolution electrospray ionisation (ESI) mass spectra were recorded on a Micromass LC-ZMD single quadrupole liquid chromatograph–mass spectrometer whereas high-resolution measurements were conducted on an LCT Premier time-of-flight instrument. Low- and high-resolution EI mass spectra were recorded on an Autospec Premier Micromass magnetic-sector machine. Optical rotations were recorded in $CHCl_3$ at 20°C on a Perkin–Elmer Model 343 polarimeter using a cell of 1 dm in length. Melting points were measured on an Optimelt automated melting point system 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). Flash chromatographic separations were carried out following protocols defined by Still et al.[16] with silica gel 60 (40–63 μm) 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), methanol, and dichloromethane were dried using a Glass Contour solvent purification system that is based on a technology originally described by Grubbs et al.[17] Where necessary, reactions were performed under an argon atmosphere.

Specific Synthetic Transformations

*(3aS,5S,12cS)-5-[(*tert*-Butyldiphenylsilyl)oxy]-2,3,3a,4,5,12c-hexahydro-[1,3]dioxolo-[4′,5′:6,7]isochromeno[3,4-g]indol-7(1*H*)-one (**19**)*

A magnetically stirred solution of amine **18**[12] (300 mg, 0.55 mmol) in degassed benzene (20 mL) maintained at 18°C under an atmosphere of nitrogen was treated, in portions, with NBS (108 mg, 0.61 mmol, 1.1 mol equiv.). After a further 0.5 h the reaction mixture was placed in an oil bath heated at 85°C then treated, via syringe pump over 0.83 h, with a solution of tri-*n*-butyltin hydride (194 μL, 0.72 mmol, 1.3 mol equiv.) and AIBN (11.5 mg, 0.07 mmol, 0.13 mol equiv.) in benzene (5 mL). After a further 2 h the ensuing mixture was cooled to 18°C then concentrated under reduced pressure. The resulting orange oil was subjected to flash chromatography (silica, 2 % v/v ammonia-saturated methanol/dichloromethane elution). Concentration of the appropriate fractions (R_f 0.4) gave *compound **19*** (246 mg, 83 %) as a white foam, $[\alpha]_D^{20}$ −3.95 (*c* 1.0, $CHCl_3$). Found: *m/z* 540.2206 $(M + H)^+$; $C_{32}H_{33}NO_5Si$ requires 540.2206 $(M + H)^+$. δ_H (400 MHz, $CDCl_3$) 7.75–7.65 (complex m, 4H), 7.48–7.21 (complex m, 8H), 6.04 (m, 2H), 4.42 (t, *J* 3.0, 1H), 3.96 (d, *J* 6.0, 1H), 3.20 (m, 1H), 3.05 (m, 1H), 2.88

(m, 1H), 2.19 (m, 1H), 1.71 (m, 1H), 1.53 (m, 2H), 1.06 (s, 9H) (signal due to N–H group proton not observed). δ_C (100 MHz, $CDCl_3$) 160.9 153.7 151.9 148.2 135.9(1), 135.8(7), 134.8, 133.8, 133.2, 129.7(1), 129.6(5), 127.7, 127.5, 116.3, 111.2, 107.3, 103.5, 102.2, 66.7, 56.6, 46.2, 33.7, 32.7, 31.4, 27.0, 19.4. ν_{max} (KBr)/cm^{-1} 2929, 2856, 1716, 1503, 1482, 1416, 1254, 1111, 1070, 1035, 937, 762. *m/z* (ESI, +ve) 562 ($[M + Na]^+$, 6 %), 540 ($[M + H]^+$, 50), 267 (100).

*(3aS,5S,12cS)-5-Hydroxy-2,3,3a,4,5,12c-hexahydro-[1,3]dioxolo[4′,5′:6,7]isochromeno[3,4-g]indol-7(1H)-one (**20**)*

A magnetically stirred solution of compound **19** (215 mg, 0.4 mmol) in THF (40 mL) maintained under an atmosphere of nitrogen was cooled to 0°C then treated with tetra-*n*-butylammonium fluoride (0.8 mL of a 1 M solution in THF, 0.8 mmol, 2.0 mol equiv.). The ensuing mixture was warmed to 18°C, stirred at this temperature for 18 h then quenched with sodium bicarbonate (5 mL of a saturated aqueous solution) and diluted with dichloromethane (3 × 10 mL). The combined organic extracts were washed with brine (3 × 10 mL) before being dried (Na_2SO_4), filtered, and then concentrated under reduced pressure to afford a light-yellow oil. Subjecting this material to flash chromatography (silica, 4 % v/v ammonia-saturated methanol/dichloromethane) and concentration of the appropriate fractions (R_f 0.4) gave *compound **20*** (114 mg, 95 %) as a white, crystalline solid, mp 163°C. $[\alpha]_D^{20}$ +82.5 (*c* 1.0, $CHCl_3$). Found: *m/z* 302.1027 $(M + H)^+$; $C_{16}H_{15}NO_5$ requires 302.1028 $(M + H)^+$. δ_H (400 MHz, $CDCl_3$) 7.33 (s, 1H), 7.17 (s, 1H), 6.06 (s, 1H), 6.03 (s, 1H), 4.43 (s, 1H), 3.76 (d, *J* 6.0, 1H), 3.25 (m, 1H), 3.01 (m, 1H), 2.69 (m, 1H), 2.13 (m, 1H), 1.90–1.71 (complex m, 2H), 1.59 (m, 1H) (signals due to N–H and O–H group protons not observed). δ_C (100 MHz, $CDCl_3$) 161.3, 153.7, 152.3, 148.1, 134.6, 115.6, 110.9, 107.1, 103.3, 102.3, 64.3, 56.4, 46.1, 32.7, 32.5, 31.2. ν_{max} (KBr)/cm^{-1} 3416, 3330, 2927, 1706, 1654, 1502, 1483, 1418, 1282, 1255, 1115, 1037. *m/z* (ESI, +ve) 324 ($[M + Na]^+$, 13 %) 302 ($[M + H]^+$, 22), 267 (100), 242 (60), 241 (48).

*(3aS,12cS)-1,2,3,3a,4,12c-Hexahydro-[1,3]dioxolo[4′,5′:6,7]isochromeno[3,4-g]indole-5,7-dione (**21**)*

Manganese dioxide (455 mg, 5.2 mmol, 15 mol equiv.) was added in one portion to a magnetically stirred solution of alcohol **20** (105 mg, 0.35 mmol) in dichloromethane (25 mL). The ensuing mixture was heated to 30°C for 22 h while being maintained under a nitrogen atmosphere then cooled to 18°C before being filtered through a pad of Celite™. The filtrate was concentrated under reduced pressure and the resulting brown oil subjected to flash chromatography (silica, ~2–3 % v/v ammonia-saturated methanol/dichloromethane). Concentration of the appropriate fractions (R_f 0.5) gave *compound **21*** (81 mg, 78 %) as a white solid, mp 142–143°C. $[\alpha]_D^{20}$ +88.8 (*c* 1.0, $CDCl_3$). Found: *m/z* 300.0871 $(M + H)^+$; $C_{16}H_{13}NO_5$ requires 300.0872 $(M + H)^+$. δ_H (400 MHz, $CDCl_3$) 7.67 (s, 1H), 7.42 (s, 1H), 6.16 (m, 2H), 4.30 (d, *J* 4.0, 1H), 3.32 (m, 1H), 3.15 (m, 1H), 2.90 (m, 1H), 2.73–2.62 (complex m, 2H), 2.20 (m, 1H), 1.84 (broad s, 1H), 1.71 (m, 1H). δ_C (100 MHz, $CDCl_3$) 188.7, 159.3, 153.9, 150.5, 143.1, 132.5, 124.6, 119.3, 108.3, 104.7, 102.8, 56.0, 46.2, 39.3, 37.4, 31.5. ν_{max} (KBr)/cm^{-1} 3349, 2931, 2876, 1714, 1677, 1501, 1484, 1416, 1322, 1274, 1254, 1145, 1026. *m/z* (ESI, +ve) 621 ($[2M + Na]^+$, 77 %), 599 ($[2M + H]^+$, 99), 322 ($[M + Na]^+$, 46), 300 ($[M + H]^+$, 80), 283 (100).

*(3aS,5R,12cS)-5-Hydroxy-2,3,3a,4,5,12c-hexahydro-[1,3]dioxolo[4′,5′:6,7]isochromeno[3,4-g]indol-7(1H)-one (**22**)*

A magnetically stirred solution of ketone **21** (73 mg, 0.25 mmol) and $CeCl_3 \cdot 7H_2O$ (92 mg, 0.38 mmol, 1.5 equiv.) in methanol (10 mL) was cooled to −78°C and, after 0.25 h, treated with sodium borohydride (11.3 mg, 0.03 mmol, 1.2 mol equiv.) then, after 0.03 h, with sodium bicarbonate (2 mL of a saturated aqueous solution). The resulting mixture was extracted with dichloromethane (5 × 10 mL), the combined organic phases were dried ($MgSO_4$), filtered, and concentrated under reduced pressure, with the residue thus obtained being subjected to flash chromatography (silica, 96 : 4 v/v dichloromethane/ammonia-saturated methanol). Concentration of the appropriate fractions (R_f 0.4) gave *compound **22*** (73 mg, 99 %) as a white, crystalline solid, mp 168–169°C. $[\alpha]_D^{20}$ +83.9 (*c* 1.0, $CDCl_3$). Found: *m/z* 302.1031 $(M + H)^+$; $C_{16}H_{15}NO_5$ requires 302.1028 $(M + H)^+$. δ_H (400 MHz, $CDCl_3$) 7.57 (s, 1H), 7.34 (s, 1H), 6.10 (m, 2H), 4.65 (dd, *J* 12.0, 6.0, 1H), 3.86 (d, *J* 3.0, 1H), 3.32 (m, 1H), 3.05 (m, 1H), 2.43 (m, 1H), 2.15–2.02 (complex m, 3H), 1.78–1.63 (complex m, 2H) (signal due to N–H group proton not observed). δ_C (100 MHz, $CDCl_3$) 161.3, 154.1, 152.6, 148.2, 135.0, 115.3, 107.4, 103.5, 102.3, 65.9, 57.1, 46.0, 35.7, 33.1, 31.8 (one signal obscured or overlapping). ν_{max} (KBr)/cm^{-1} 3316, 2926, 2870, 1709, 1621, 1502, 1481, 1416, 1283, 1256, 1165, 1094, 1034. *m/z* (ESI, +ve) 324 ($[M + Na]^+$, 40 %) 302 ($[M + H]^+$, 100), 241 (35).

*(R)-2-(2-(Dimethylamino)ethyl)-4-hydroxy-3,4-dihydro-6H-[1,3]dioxolo[4′,5′:4,5]benzo-[1,2-c]chromen-6-one (**24**)*

A magnetically stirred mixture of compound **22** (42 mg, 0.14 mmol) and methyl iodide (1 mL, 16 mmol) maintained under a nitrogen atmosphere at 18°C was treated with silver(I) oxide (323 mg, 1.4 mmol) and the resulting mixture stirred in a sealed tube at 50°C for 16 h before being cooled, filtered, and concentrated under reduced pressure. The resulting yellow oil was subjected to flash chromatography (silica, 95 : 5 → 90 : 10 v/v dichloromethane/ammonia-saturated methanol gradient elution) and concentration of the relevant fractions (R_f 0.3 in 90 : 10 v/v dichloromethane/ammonia-saturated methanol) gave an unstable oil (30 mg), a portion of which crystallised on standing. A crystal of this material was subjected to single-crystal X-ray analysis and this revealed it to be *compound **24***. The very small quantities of compound **24** obtained by this means precluded the acquisition of any other spectral data.

*(3aS,5R,12cS)-5-Hydroxy-2,3,3a,4,5,12c-hexahydro-[1,3]dioxolo-[4′,5′:6,7]isochromeno[3,4-g]indol-7(1H)-one [(+)-**2**, (+)-Narseronine]*

A magnetically stirred solution of alcohol **22** (18.6 mg, 0.06 mmol) in dry THF (2 mL) maintained at 0°C under a nitrogen atmosphere, was treated, in portions, with potassium hydride (32 mg of a 30 % dispersion in mineral oil, 0.24 mmol, 4.0 mol equiv.) and then with methyl iodide (30 μL, 0.48 mmol, 8.0 mol equiv.) After a further 4 h the reaction mixture was quenched with NH_4Cl (2 mL of a saturated aqueous solution) and the separated aqueous phase extracted with dichloromethane (3 × 10 mL). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated under reduced pressure. The light-yellow oil thus obtained was subjected to flash chromatography (silica, 95 : 5 v/v, dichloromethane/ammonia-saturated methanol

elution) and concentration of the appropriate fractions (R_f 0.4) gave (+)-narseronine [(+)-**2**] (16.8 mg, 83 %) as a white, crystalline solid, mp 165–166°C [lit.[8] for (−)-enantiomer 167–168°C]. $[\alpha]_D^{20}$ +21.0 (*c* 0.3, $CHCl_3$). Found: *m/z* 330.1342 $(M + H)^+$; $C_{18}H_{19}NO_5$ requires 330.1341 $(M + H)^+$. δ_H (400 MHz, $CDCl_3$) 7.67 (s, 1H), 7.28 (s, 1H), 6.13 (m, 2H), 4.22 (t, *J* 6.0, 1H), 3.82 (broad s, 1H), 3.57 (s, 3H), 3.07 (m, 1H), 2.78 (m, 1H), 2.64 (m, 1H), 2.44 (s, 3H), 2.25–2.10 (complex m, 2H), 2.01 (m, 1H), 1.90 (m, 1H). δ_C (100 MHz, $CDCl_3$) 161.5, 153.7, 152.7, 148.3, 135.2, 116.4, 108.5, 107.8, 103.3, 102.4, 75.0, 62.0, 58.2, 54.3, 42.1, 35.0, 31.4, 29.5. ν_{max} (KBr)/cm^{-1} 3449, 2927, 1718, 1623, 1502, 1482, 1413, 1282, 1256, 1161, 1102, 1035. *m/z* (ESI, +ve) 352 ($[M + Na]^+$, 8 %), 330 ($[M + H]^+$, 100), 298 (20). The ^{1}H NMR, ^{13}C NMR, and infrared spectral data presented above were in good agreement with those reported for the natural product[7] and for the synthetically derived (−)-narseronine.[8] The only minor discrepancy was observed in the ^{13}C NMR spectra. In particular, the signal reported at 111.5 ppm in the spectrum of the synthetically derived (−)-enantiomer was replaced by one at 108.5 ppm in that of (+)-**2**. This difference is attributed to the differing acidities of the media in which the samples were analysed.

X-Ray Crystallographic Study

Crystallographic Data

*Compound (+)-**2***

$C_{18}H_{19}NO_5$, *M* 329.35, *T* 150 K, tetragonal, space group $P4_12_12$, *Z* 8, *a* 9.0508(2), *b* 9.0508(2), *c* 38.9156(17) Å, *V* 3187.85(17) Å^3, D_x 1.372 g cm^{-3}, 3137 unique data ($2\theta_{max}$ 146°), *R* 0.063 [for 2832 reflections with $I > 2.0\sigma(I)$], *Rw* 0.135 (all data), *S* 1.04.

*Compound **20***

$3(C_{16}H_{15}NO_5)\cdot CH_2Cl_2\cdot CH_4O$, *M* 1020.87, *T* 200 K, monoclinic, space group $P2_1$, *Z* 2, *a* 10.4126(15), *b* 14.0062(19), *c* 15.8996(18) Å, β 103.807(8)°, *V* 2251.8(5) Å^3, D_x 1.506 g cm^{-3}, 4142 unique data ($2\theta_{max}$ 50.2°), *R* 0.102 [for 2507 reflections with $I > 2.0\sigma(I)$], *Rw* 0.285 (all data), *S* 1.01.

*Compound **22***

$C_{16}H_{15}NO_5$, *M* 301.30, *T* 200 K, orthorhombic, space group $P2_12_12_1$, *Z* 4, *a* 7.2115(2), *b* 12.2738(3), *c* 14.9955(5) Å, *V* 1327.29(7) Å^3, D_x 1.508 g cm^{-3}, 1764 unique data ($2\theta_{max}$ 55°), *R* 0.035 [for 1543 reflections with $I > 2.0\sigma(I)$], *Rw* 0.084 (all data), *S* 0.99.

*Compound **24***

$C_{18}H_{19}NO_5$, *M* 329.35, *T* 200 K, orthorhombic, space group $P2_12_12_1$, *Z* 4, *a* 7.9212(7), *b* 8.8428(8), *c* 22.4138(19) Å, *V* 1570.0(2) Å^3, D_x 1.393 g cm^{-3}, 1615 unique data ($2\theta_{max}$ 50°), *R* 0.064 [for 1109 reflections with $I > 2.0\sigma(I)$], *Rw* 0.137 (all data), *S* 1.08.

Structure Determination

Images were measured on a Nonius Kappa CCD diffractometer (MoKα, graphite monochromator, λ 0.71073 Å) and data extracted using the *DENZO* package[18] or an Agilent SuperNova CCD diffractometer (CuKα, mirror monochromator, λ 1.54184 Å) and data extracted using the *CrysAlis* package.[19] Structure solutions were by direct methods (*SIR92*).[20] The structures of compounds (+)-**2**, **20**, **22**, and **24** were refined using the *CRYSTALS* program package.[21] Atomic coordinates, bond lengths and angles, and displacement parameters have been deposited at the Cambridge Crystallographic Data Centre (CCDC nos. 1020370, 944982, 948651, and 1017935 for compounds (+)-**2**, **20**, **22**, and **24**, respectively). 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.

Supplementary Material

The anisotropic displacement ellipsoid plots derived from the single-crystal X-ray structures of compounds (+)-**2**, **20**, **22**, and **24** together with ^{1}H and ^{13}C NMR spectra of compounds (+)-**2**, **19**, **20**, **21**, and **22** are available on the Journal's website.

Acknowledgements

We thank the Australian Research Council and the Institute of Advanced Studies for generous financial support. The very useful ongoing advice provided by Dr Brett Schwartz is gratefully acknowledged.

References

[1] For key early studies in this area, see: (a) D. T. Gibson, J. R. Koch, R. E. Kallio, *Biochemistry* **1968**, *7*, 2653. doi:10.1021/BI00847A031
(b) D. T. Gibson, J. R. Koch, C. L. Schuld, R. E. Kallio, *Biochemistry* **1968**, *7*, 3795. doi:10.1021/BI00851A003
(c) D. T. Gibson, V. Subramanian, in *Microbial Degradation of Organic Compounds* (Ed. D. T. Gibson) **1984**, pp. 181–252 (Marcel Dekker: New York, NY).
(d) G. J. Zylstra, D. T. Gibson, *J. Biol. Chem.* **1989**, *264*, 14940.

[2] For recent reviews on the production and/or synthetic utility of *cis*-1,2-dihydrocatechols, see: (a) T. Hudlicky, D. Gonzalez, D. T. Gibson, *Aldrichim Acta* **1999**, *32*, 35.
(b) R. A. Johnson, *Org. React.* **2004**, *63*, 117.
(c) D. R. Boyd, T. D. H. Bugg, *Org. Biomol. Chem.* **2006**, *4*, 181. doi:10.1039/B513226F
(d) T. Hudlicky, J. W. Reed, *Synlett* **2009**, 685. doi:10.1055/S-0028-1087946
(e) T. Hudlicky, J. W. Reed, *Chem. Soc. Rev.* **2009**, *38*, 3117. doi:10.1039/B901172M
(f) J. Duchek, D. R. Adams, T. Hudlicky, *Chem. Rev.* **2011**, *111*, 4223. doi:10.1021/CR1004138
(g) M. G. Banwell, A. L. Lehmann, R. S. Menon, A. C. Willis, *Pure Appl. Chem.* **2011**, *83*, 411. doi:10.1351/PAC-CON-10-10-21
(h) D. J.-Y. D. Bon, B. Lee, M. G. Banwell, I. A. Cade, *Chim. Oggi* **2012**, *30* (*No. 5, Chiral Technologies Supplement*), 22.

[3] For a useful point of entry into the literature on chemoenzymatic synthesis, see: H. Gröger, *ChemCatChem* **2011**, *3*, 239. doi:10.1002/CCTC.201100018

[4] The enantiomeric forms (including *ent*-**1**) of just a small fraction of the ~400 known *cis*-1,2-dihyrocatechols have been reported to date:
(a) D. R. Boyd, N. D. Sharma, S. A. Barr, H. Dalton, J. Chima, G. Whited, R. Seemayer, *J. Am. Chem. Soc.* **1994**, *116*, 1147. doi:10.1021/JA00082A053
(b) C. C. R. Allen, D. R. Boyd, H. Dalton, N. D. Sharma, I. Brannigan, N. A. Kerley, G. N. Sheldrake, S. C. Taylor, *J. Chem. Soc., Chem. Commun.* **1995**, 117. doi:10.1039/C39950000117

[5] T. Hudlicky, J. D. Price, F. Rulin, T. Tsunoda, *J. Am. Chem. Soc.* **1990**, *112*, 9439. doi:10.1021/JA00181A081

[6] (a) M. G. Banwell, C. Chun, A. J. Edwards, M. M. Vögtle, *Aust. J. Chem.* **2003**, *56*, 861. doi:10.1071/CH03112
(b) M. G. Banwell, A. J. Edwards, G. J. Harfoot, K. A. Jolliffe, *Tetrahedron* **2004**, *60*, 535. doi:10.1016/J.TET.2003.10.122
(c) C. E. Dietinger, M. G. Banwell, M. J. Garson, A. C. Willis, *Tetrahedron* **2010**, *66*, 5250. doi:10.1016/J.TET.2010.04.056

[7] N. B. Pigni, S. Berkov, A. Elamrani, M. Benaissa, F. Viladomat, C. Codina, J. Bastida, *Molecules* **2010**, *15*, 7083. doi:10.3390/MOLECULES15107083
[8] B. D. Schwartz, M. G. Banwell, I. A. Cade, *Tetrahedron Lett.* **2011**, *52*, 4526. doi:10.1016/J.TETLET.2011.06.050
[9] (a) M. T. Jones, B. D. Schwartz, A. C. Willis, M. G. Banwell, *Org. Lett.* **2009**, *11*, 3506. doi:10.1021/OL901364N
(b) B. D. Schwartz, M. T. Jones, M. G. Banwell, I. A. Cade, *Org. Lett.* **2010**, *12*, 5210. doi:10.1021/OL102249Q
[10] D. H. R. Barton, S. W. McCombie, *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574. doi:10.1039/P19750001574
[11] For recent applications of Raney-cobalt in the selective reduction of nitriles, see: (a) S. H. Tan, M. G. Banwell, A. C. Willis, T. A. Reekie, *Org. Lett.* **2012**, *14*, 5621. doi:10.1021/OL3026846
(b) T. A. Reekie, M. G. Banwell, A. C. Willis, *J. Org. Chem.* **2012**, *77*, 10773. doi:10.1021/JO302132D
[12] L. V. White, B. D. Schwartz, M. G. Banwell, A. C. Willis, *J. Org. Chem.* **2011**, *76*, 6250. doi:10.1021/JO201005D
[13] M. G. Banwell, M. T. Jones, T. A. Reekie, B. D. Schwartz, S. H. Tan, L. V. White, *Org. Biomol. Chem.* **2014**, *12*, 7433. doi:10.1039/C4OB00917G
[14] A. L. Gemal, J. L. Luche, *J. Am. Chem. Soc.* **1981**, *103*, 5454. doi:10.1021/JA00408A029
[15] For a relevant recent paper dealing with arene hydrates, see: D. R. Boyd, N. D. Sharma, V. Ljubez, P. K. M. McGeehin, P. J. Stevenson, M. Blaine, C. C. R. Allen, *Org. Biomol. Chem.* **2013**, *11*, 3020. doi:10.1039/C3OB40166A
[16] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem.* **1978**, *43*, 2923. doi:10.1021/JO00408A041
[17] A. B. Pangborn, M. A. Giardello, R. H. Grubbs, R. K. Rosen, F. J. Timmers, *Organometallics* **1996**, *15*, 1518. doi:10.1021/OM9503712
[18] *DENZO–SMN*: Z. Otwinowski, W. Minor, in *Methods in Enzymology, Volume 276: Macromolecular Crystallography, Part A* (Eds C. W. Carter, Jr, R. M. Sweet) **1997**, pp. 307–326 (Academic Press: New York, NY).
[19] Agilent Technologies, *CrysAlisPro Version 1.171.37.33d* (release 23–04–2014 CrysAlis171.NET) (compiled 23 April 2014, 17:37:27).
[20] *SIR92*: A. Altomare, G. Cascarano, C. Giacovazzo, A. Guagliardi, M. C. Burla, G. Polidori, M. Camalli, *J. Appl. Crystallogr.* **1994**, *27*, 435.
[21] P. W. Betteridge, J. R. Carruthers, R. I. Cooper, K. Prout, D. J. Watkin, *J. Appl. Crystallogr.* **2003**, *36*, 1487. doi:10.1107/S0021889803021800