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A chemoenzymatic total synthesis of the Amaryllidaceae alkaloid narseronine

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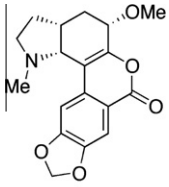
ABSTRACT

A 15-step and fully stereocontrolled total synthesis of the title alkaloid **1** has been accomplished using the enantiomerically pure and enzymatically-derived *cis*-1,2-dihydrocatechol **2** as starting material. The final and pivotal step involved the intramolecular hetero-Michael addition of secondary amine **16** to a tethered enone moiety followed by trapping of the resulting enolate through its reaction with an adjacent ester residue.

In 2010 Bastida and colleagues reported[1] the isolation of the alkaloid narseronine (**1**) from the flowering plant *Narcissus serotinus* L. which grows in dry coastal regions of many parts of the Mediterranean.[1] The illustrated structure, including relative stereochemistry, was proposed on the basis of the derived 1- and 2-D ^{1}H and ^{13}C NMR, UV, infra-red, and mass spectral data.[1,2] As such, the compound appears to be a member of the masanane- or lycorenine-type subclass of Amaryllidaceae alkaloids and one that possesses an unsaturated δ-lactone residue as a notable feature. No biological evaluation of the title compound appears to have been undertaken. However, other compounds within the subclass and other natural products possessing related structures display various interesting biological effects, including antifungal, antitumour, and apoptosis-inducing activities.[3] Accordingly, we sought to develop an enantioselective total synthesis of narseronine in order to obtain material for biological evaluation and to confirm the assigned structure. Herein we report the first total synthesis of the title alkaloid.

The opening stages of our synthesis of compound **1** (Scheme 1) involve the same sequence of reactions as employed during the course of assembling the framework originally (and erroneously) assigned to the alkaloid nobilisitine A.[4] Details are re-iterated here so as to provide the reader with a self-contained overview of the entirety of the present synthesis. Thus, as with our previous work,[4] the starting material used was *cis*-1,2-dihydrocatechol **2**, an enantiomerically pure compound available in large quantity via the whole-cell biotransformation of bromobenzene.[5] This diol **2** was converted, under standard conditions, into the well known[6] acetonide **3** (93%) that was then subjected to electrophilic epoxidation with *m*-chloroperbenzoic acid (*m*-CPBA). The resulting and previously reported[6] epoxide **4** (95%), which was obtained in a completely regio- and diastereo-selective manner, was then treated with the acetonitrile anion and thereby affording the γ-hydroxynitrile **5**[4,7] (96%) as the only isolable product of reaction. Subjection of the latter compound to a Barton–McCombie deoxygenation reaction[8] provided, via the intermediate xanthate ester **6** (94%), the desired methylene-containing derivative **7** (82% from **5**). Suzuki–Miyaura cross-coupling[9] of compound **7** with the readily available boronate ester **8**[4,7] then gave the arylated cyclohexene **9**[4,7] (75%), a key intermediate associated with our recently reported[7] synthesis of a lycorine degradation product.



narseronine (1)

The nitrile moiety within compound **9** was reduced to the corresponding primary amine **10** in a completely chemoselective manner using dihydrogen in the presence of Raney-cobalt.[10] Reaction of the latter compound with Alloc-Cl in the presence of pyridine gave carbamate **11** (88% from **9**) that could be N-methylated by treating it with lithium hexamethyldisilazide (LiHMDS) and methyl iodide. Compound **12** was thereby obtained in 98% yield.

The conversion of compound **12** into target **1** was carried out using the reaction sequence shown in Scheme 2. So, treatment of acetonide/lactone **12** with aqueous acetic acid resulted in cleavage of the acetonide unit but the subsequent and desired lactonization

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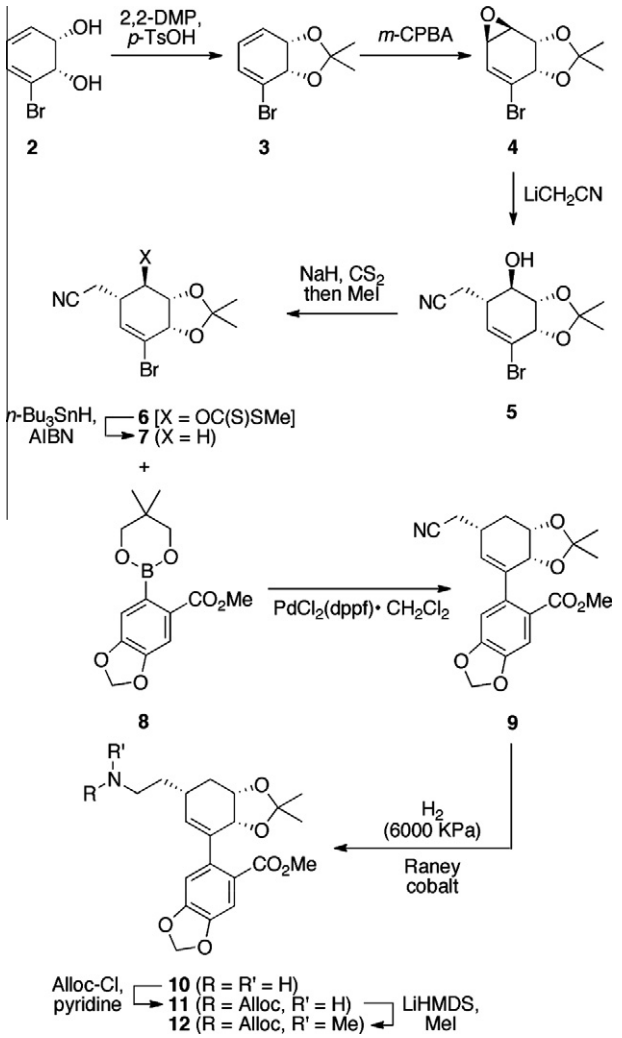
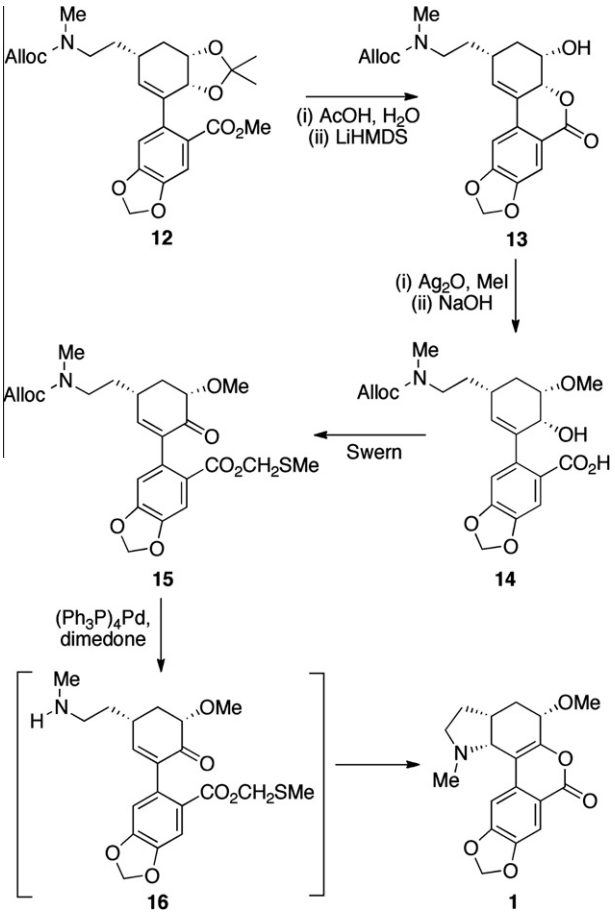


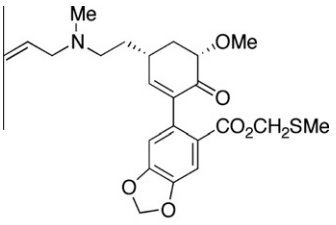
Scheme 1.



Scheme 2.

process proved sluggish. Accordingly, the crude hydrolysis product was treated with LiHMDS and the target compound **13** was thereby obtained in 77% yield. Irvine–Purdie methylation[11] of alcohol **13** gave the corresponding ether/lactone (72%) that was immediately subjected to saponification with sodium hydroxide and thus forming, after acidic work-up, hydroxy acid **14** (68% from **13**) that was rather prone to relactonization. Upon subjecting compound **14** to Swern oxidation conditions the allylic alcohol was converted into the corresponding enone and the free carboxylic acid was transformed into the methylthiomethyl ester[12] such that compound **15** (48%) was obtained together with quantities of the precursor lactone *O*-methyl ether (29%).

In the final step of the reaction sequence, carbamate **15** was treated with $(Ph_3P)_4Pd$ and an excess of dimedone.[13] As a result the target compound narseronine (**1**) was obtained in 82% yield. Presumably compound **1** is formed through the secondary amine **16** (arising from deprotection of carbamate **15**) engaging in a spontaneous intramolecular hetero-Michael addition to the pendant enone moiety with the resulting enolate then undergoing an intermolecular acylation reaction involving the adjacent ester group. Accompanying target **1** were variable but small amounts of the chromatographically separable allyl amine **17** that presumably arises through attack of secondary amine **16** on the π-allyl palladium complex arising from deprotection of carbamate **15**. By using a 10-fold excess of dimedone to trap the intermediate π-allyl complex it was possible to eliminate almost completely the formation of this by-product.



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All of the spectral data derived from lactone **1** were in complete accord with the assigned structure but final confirmation of this followed from a single-crystal X-ray analysis.[14] The ORTEP arising from this analysis is shown in Figure 1.

A comparison of the ^{1}H and ^{13}C NMR spectral data derived from lactone **1** with those reported[1] for narseronine is presented in Table 1. This strongly suggests that the two compounds are the same in terms of structure and relative stereochemistry. The infra-red and mass spectral data obtained on the synthetically-derived material also matched those reported for the natural product. Unfortunately, the specific rotation of the natural product has not been reported so it is not possible to comment on the absolute configuration of this alkaloid.[15]

Table 1
Comparison of the ^{13}C and ^{1}H NMR data recorded for synthetically-derived narseronine and the natural product

^{13}C NMR data (δ_C)		^{1}H NMR data (δ_H)	
Synthetic **1**[a]	Narseronine[b]	Synthetic **1**[c]	Narseronine[d]
161.5	161.5	7.68, s, 1H	7.66, s, 1H
153.5	153.8	7.28, s, 1H	7.29, s, 1H
152.3	152.9	6.13, d, *J* = 1.2 Hz, 1H	6.12, d, *J* = 1.2 Hz, 1H
148.1	148.4	6.11, d, *J* = 1.2 Hz, 1H	6.10, d, *J* = 1.2 Hz, 1H
135.1	135.1	4.22, t, *J* = 6.0 Hz, 1H	4.22, t, *J* = 6.1 Hz, 1H
116.3	116.4	3.91, d, *J* = 7.0 Hz, 1H[e]	3.94, d, *J* = 6.4 Hz, 1H
111.5	110.9	3.57, s, 3H	3.57, s, 3H
107.6	107.9	3.07, dt, *J* = 11.0 and 7.6 Hz, 1H	3.05, dt, *J* = 11.0 and 7.6 Hz, 1H
103.1	103.3	2.78, m, 1H[e]	2.81, m, 1H
102.2	102.4	2.63, m, 1H[e]	2.64, m, 1H
74.8	75.0	2.43, s, 3H	2.41, s, 3H
61.9	61.7	2.23–2.10, complex m, 2H	2.22–2.13, m, 2H
58.0	58.3	2.03, dt, *J* = 13.0 and 6.0 Hz, 1H	2.01, dt, *J* = 13.5 and 5.5 Hz, 1H
54.1	54.3	1.89, ddd, *J* = 13.0, 8.0 and 4.4 Hz, 1H	1.90, ddd, *J* = 12.6, 8.3 and 4.2 Hz, 1H
42.1	41.8		
34.7	35.1		
31.2	31.4		
29.3	29.6		

[a] Data recorded in $CDCl_3$ at 100 MHz.
[b] Data obtained from spectrum provided by Professor Bastida and recorded in $CDCl_3$ at 125 MHz.
[c] Data recorded in $CDCl_3$ at 400 MHz.
[d] Data obtained from Ref. 1 and recorded in $CDCl_3$ at 500 MHz.
[e] The chemical shift of this resonance varied somewhat from run-to-run.

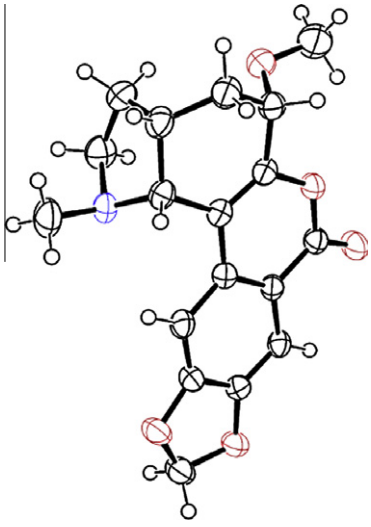

Figure 1. ORTEP derived from the single-crystal X-ray analysis of compound **1**. Displacement ellipsoids are drawn at the 50% probability level. Hydrogen atoms are shown as spheres of arbitrary radius.

Acknowledgements

We thank the Institute of Advanced Studies and the Australian Research Council for financial support. Professor Jaume Bastida (University of Barcelona) is thanked for providing copies of the ^{1}H and ^{13}C NMR spectra recorded on naturally-derived narseronine.

Supplementary data

Supplementary data (experimental procedures and product characterization for compounds **13**, **13** *O*-methyl ether, **14**, **15**, and **1** as well as the X-ray crystallographic data for compound **1**) associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2011.06.050.

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14. X-ray crystal data for compound **1** can be found in the Supplementary data. Crystallographic data (excluding structure factors) for compound **1** have been deposited with the Cambridge Crystallographic Data Centre (CCDC no. 822115). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).
15. The specific rotation recorded for synthetically-derived material was −25.4 (*c* 1.6, $CDCl_3$).