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A Noncarbohydrate Based Approach to Polyhydroxylated Pyrrolidizines: Total Syntheses of the Natural Products Hyacinthacine A_1 and 1-Epiaustraline

Timothy J. Donohoe,*,† Herman O. Sintim,† and Jackie Hollinshead‡

Department of Chemistry, Chemistry Research Laboratory, University of Oxford, Mansfield Road, Oxford, OX1 3TA, United Kingdom, and MLNpharma Limited, Plas Gogerddan, Aberystwyth, Ceredigion SY23 3EB, United Kingdom

timothy.donohoe@chem.ox.ac.uk

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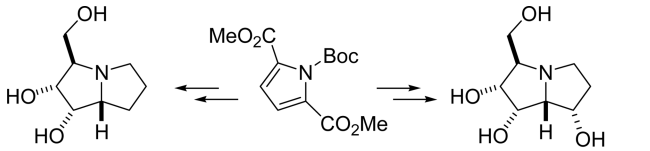

A flexible route to polyhydroxylated pyrrolizidine alkaloids is described, starting from commercially available *N*-Boc pyrrole and using a partial reduction as the key step. Tactics for varying the stereochemistry around the ring by choice of partial reduction conditions are discussed and methods for constructing the bicyclic ring system of the pyrrolizidine targets are examined. Intramolecular S_N2 type displacement reactions were found to be an efficient way of forming the requisite bicyclo ring systems while iodine-promoted cyclizations proved unsuitable. A first synthesis of hyacinthacine A_1 is described that also confirmed the structure of the natural product, and a short stereoselective synthesis of 1-epiaustraline is also discussed in detail.

Introduction

The central role that glycosidase enzymes play in the cell means that compounds which specifically inhibit these various enzymes are of pharmacological relevance. The search for effective glycosidase inhibitors is driven by potential applications in the treatment of various diseases such as cancer, diabetes, and some viral infections. A wide range of polyhydroxylated pyrrolidine and pyrrolizidine natural products have been isolated and have drawn considerable interest in recent years, mainly because of their ability to inhibit several glycosidase enzymes.[1] The polyhydroxylated pyrrolizidine natural products in question are all based on the monocyclic glycosidase inhibitor DMDP, Figure 1. The diversity contained within natural products such as the hyacinthacines, australines, and casuarines derives not only from stereochemical isomerism (compare **2** with **5**) but also from the substitution pattern of the second pyrrolidine ring.[2] This is best illustrated by comparison of the bicycloring system of one of the simplest pyrrolizidines (hyacinthacine A_1) with one of the most complex (hyacinthacine C_1).

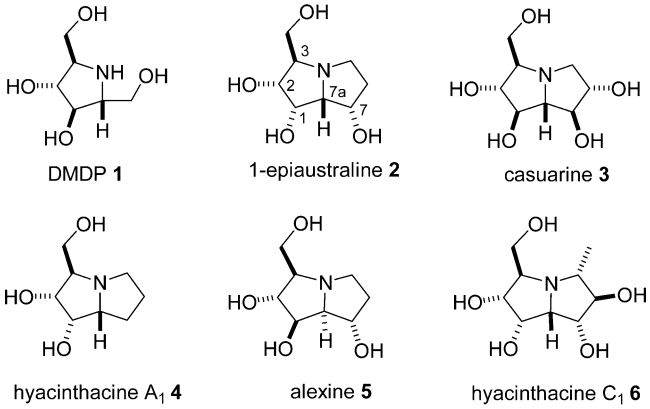

FIGURE 1. Structural and stereochemical variations of naturally occurring pyrrolizidines.

* Address correspondence to this author.
† University of Oxford.
‡ MLNpharma Limited.

(1) (a) *Iminosugars as Glycosidase Inhibitors. Nojirimycin and Beyond*; Stutz, A. E., Ed.; Wiley-VCH: Weinheim, Germany, 1999. (b) Butters, T. D.; Dwek, R. A.; Platt, F. M. *Chem. Rev.* **2000**, *100*, 4683.

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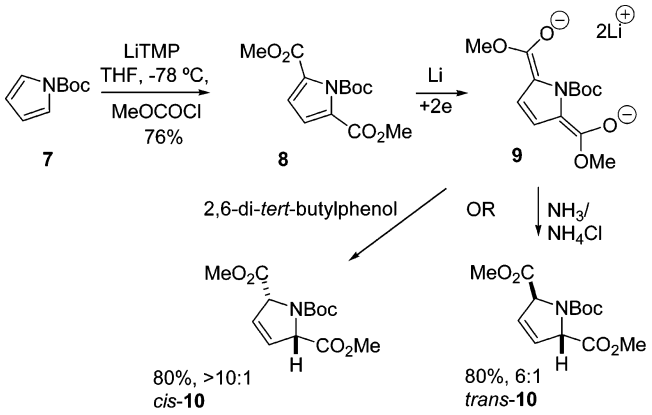
SCHEME 1

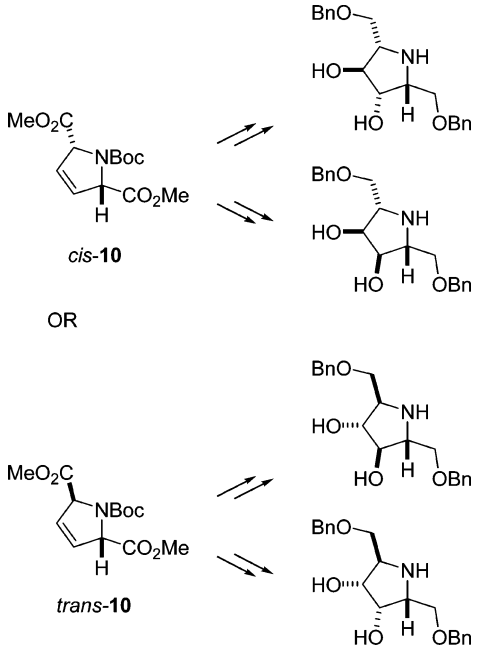


Clearly, the development of a concise and flexible synthetic strategy that accesses the polyhydroxylated pyrrolidine motif will find synthetic and biological utility; naturally, various research groups have already developed sophisticated programs to access these biologically active molecules.[3]

The most common approach to polyhydroxylated pyrrolizidine alkaloids involves the chiral pool, and uses a variety of starting materials derived from (mainly) carbohydrates and also amino acids.[3,4] Recently, Han has reported a de novo approach to hydroxylated pyrrolidines using the Sharpless aminohydroxylation reaction as a key step for setting the absolute and relative stereochemistry of the targets.[5] On one hand, syntheses based on the chiral pool can be devastatingly efficient for the formation of a particular isomer of the target: however, the same approach can prove to be lengthy for the synthesis of a different isomer. In comparison, de novo approaches have to rely on methods for forming the relevant stereogenic centers with high levels of stereoselectivity; this is not always easy. Our interests lie in the de novo route to polyhydroxylated pyrrolidines and the development of a succinct, flexible, and stereoselective synthetic strategy to access these glycosidase inhibitors.

Herein, we describe a modular approach to the syntheses of polyhydroxylated pyrrolidizines starting from readily available pyrrole **8** (obtained in one step and on a multigram scale from commercially available *N*-Boc pyrrole **7**, lithium tetramethylpiperidine, and methyl chloroformate), Scheme 1.[6] Our approach relies upon stereodivergent partial reduction of pyrrole **8**. Using previously reported methodology, compound **8** can be reduced to give either the *trans*-alkene **10** or *cis*-alkene **10** (Scheme 1) with good stereoselectivity.[6] For example, the use of lithium in ammonia (quenching with ammonium chloride) converted **8** into *trans*-**10** (6:1) whereas ammonia-free reduction with LiDBB (quenching with 2,6-di-*tert*-butylphenol) gave *cis*-**10** exclusively.

SCHEME 2



In addition, we have then been able to install geminal hydroxyl functionality at C-3,4 (post reduction) with either the cis or trans configuration; starting from either *trans*- or *cis*-**10** this sequence gives us the flexibility for substitution in the targets that we desire, Scheme 2. This early work culminated in a synthesis of (±)-DMDP (**1**).[6]

This paper will concentrate on tactics for constructing the second heterocyclic ring from the templates described above, thus forming the bicyclic unit found in the aforementioned pyrrolizidine targets. There are two biologically active targets which guided this area of research: hyacinthacine A_1[7] **4** is a polyhydroxypyrrolizidine that was isolated from the bulbs of *Muscari armeniacum* (hyacinthaceae), and is a potent inhibitor of rat intestinal lactase, with an IC_{50} value of 4.4 μM. It is also a moderate inhibitor of α-L-fucosidase and amyloglucosidase, with IC_{50} values of 46 and 25 μM, respectively. To the best of our knowledge, no synthesis of hyacinthacine A_1 has been reported in the literature and so a chemical synthesis should confirm the structure of this compound. The remaining target, 1-epiaustraline **2**, is also a polyhydroxylated pyrrolizidine produced by the plant *Castanospermum australae*;[8] it inhibits α-glucosidase amyloglucosidase (50% inhibition at 26 μM), glucosidase I, β-glucosidase, and α-mannosidase at millimolar levels.

(2) See: (a) Woramld, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **1998**, *9*, 2549. (b) Kato, A.; Adachi, I.; Miyauchi, M.; Ikeda, K.; Komae, T.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Wormald, M. R.; Fleet, G. W. J.; Asano, N. *Carbohydr. Res*. **1999**, *316*, 95; see also refs 7 and 8.

(3) For representative syntheses of australines and alexines, see: (a) White, J. D.; Hrnciar, P. *J. Org. Chem*. **2000**, *65*, 9129. (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785. (c) Yoda, H.; Katoh, H.; Takabe, K. *Tetrahedron Lett.* **2000**, *41*, 7661. For hyacinthacines see: (d) Toyao, A.; Tamura, H.; Takagi, H.; Ishibashi, H. *Synlett* **2003**, 35. (e) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron*: *Asymmetry* **2002**, *13*, 1503. (f) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron*: *Asymmetry* **2002**, *13*, 1581. For casuarines see: (g) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti *Tetrahedron Lett*. **2003**, *44*, 2315. See also ref 9.

(4) For pyroglutamate routes see: (a) Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553. (b) Ikota, N.; Nakagawa, H.; Ohno, S.; Noguchi, K.; Okuyama, K. *Tetrahedron* **1998**, *54*, 8985.

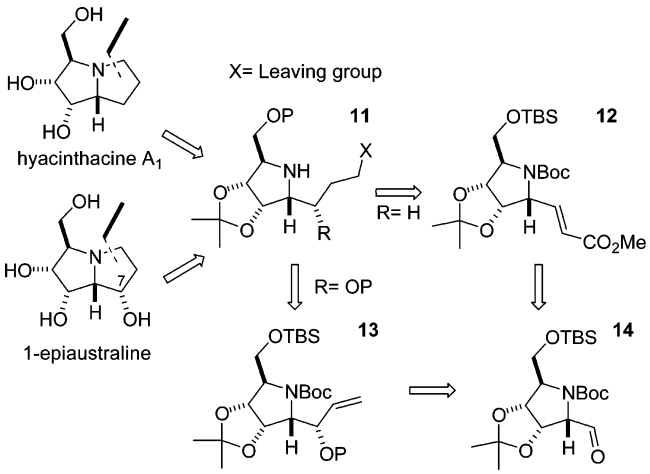
(5) Singh, S.; Hyunsoo, H. *Tetrahedron Lett.* **2004**, *45*, 6349.

(6) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999.

(7) Asano, N.; Kuori, H.; Ikeda, K.; Kizu, H.; Kameda, Y.; Kato, A.; Adachi, I.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J. *Tetrahedron*: *Asymmetry* **2000**, *11*, 1.

(8) (a) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J.; Girdhar, A.; Ramsden, L. E.; Peach, J. M.; Hegarty, M. P.; Scofield, A. M. *Phytochemistry* **1990**, *29*, 111. (b) Harris, C. M.; Harris, T. M.; Molyneux, R. J.; Tropea, J. E.; Elbein, A. D. *Tetrahedron Lett.* **1989**, *30*, 5685.

SCHEME 3



1-Epiaustraline **2** also inhibits yeast α-glucosidase (50% inhibition at 270 μM), an activity not demonstrated by other α-glucosidase inhibitors. There are now five reported syntheses of 1-epiaustraline by Denmark, Donohoe, Fleet, Ikota, and Pyne.[9]

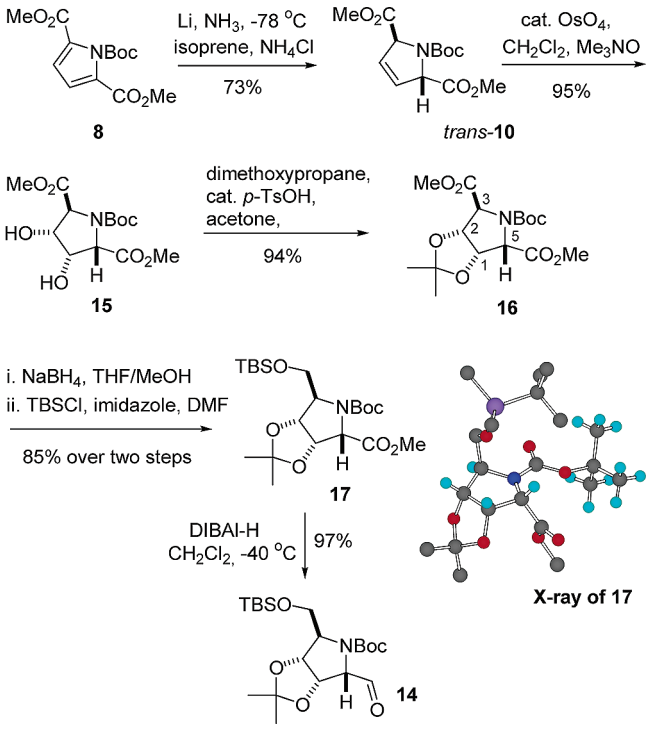
Preliminary results outlining the synthesis of 1-epiaustraline from pyrrole **7** were recently described elsewhere.[9c] We now wish to discuss here these results in full and also describe the first synthesis of hycinthacine A_1. In the longer term our aim is to develop methodology capable of accessing any diastereo or structural isomer of these pyrolizidine alkaloid targets.

Results and Discussion

Synthesis of Hyacinthacine A_1 from Pyrrole 7. Our first target was hyacinthacine A_1; we aimed to prove the utility of our methodology and also confirm the structure of the natural product. A retrosynthetic analysis of both hyacinthacine A_1 and 1-epiaustraline is shown in Scheme 3. In both cases, we envisaged an internal S_N2 type displacement on an activated form of **11** (X = halo or OMs) as being a mild and efficient way of making the pyrrolizidine skeleton. A key question revolves around the timing of activation of the terminal carbon toward nucleophilic attack: could a OMs group be formed directly (regioselectively) from an amino-alcohol precursor or must it be preformed from a primary alcohol earlier in the sequence (with the nitrogen protected) and carried through the synthesis?[4] Further disconnections on **11** lead (via **12** or **13**) back to a common precursor, the fully substituted aldehyde **14**.

So, the synthesis of hyacinthacine A_1 began with pyrrole **8**, which was transformed into racemic *trans*-**10** and then dihydroxylated under standard Poli dihydroxylation conditions (cat. OsO_4, Me_3NO, 3 equiv in CH_2Cl_2)[10] to give diol **15** in an excellent yield of 95% (Scheme 4). Standard acetonide protection of **15** then gave acetonide **16** in 94% yield and a methanolic solution of $NaBH_4$ reduced the C3 ester of **16** regioselectively to afford **17**

SCHEME 4



after subsequent TBS protection. This regioselectivity was anticipated as the C5 ester functionality in **16** was more sterically hindered because of its cis relationship to the acetonide unit; the relative stereochemistry of ester **17** was confirmed by X-ray crystal analysis (Scheme 4). Aldehyde **14** was obtained after a DIBAL-H reduction of **17** at −40 °C. Temperature control is essential here as temperatures lower than −40 °C resulted in substantial recovery of starting material whereas higher temperatures resulted in over-reduction to the corresponding primary alcohol.

With multigram quantities of aldehyde **14** in hand, the olefination step was investigated, Scheme 5. Methyl (triphenylphosphoranylidene)acetate was added to **14** in toluene and the mixture heated at reflux overnight. The major adduct **18** was obtained in near quantitative yield after evaporation of solvent and column chromatography. The alkene unit in ester **18** (Scheme 5) was assumed to be *E* configured, in line with literature precedent and a coupling constant (J = 15.8 Hz) consistent with *E* geometry.

At first, the hydrogenation of alkene **18** into saturated adduct **19** did not proceed smoothly. Using standard hydrogenation conditions (Pd/C, H_2, 1 atm), compound **19** was obtained, but contaminated with a substantial amount of desilylated compound **23**. In fact, the desilylation of silyl ethers under hydrogenation with Pd catalysis is precedented in the literature.[11] Nickel dichloride-catalyzed sodium borohydride 1,4 reduction of alkene **18**[12] also gave compound **19** but in a moderate yield of 60%. Therefore, we turned our attention back to hydrogenation conditions; changing the catalyst from Pd/C to PtO_2 afforded saturated compound **19** in quantitative

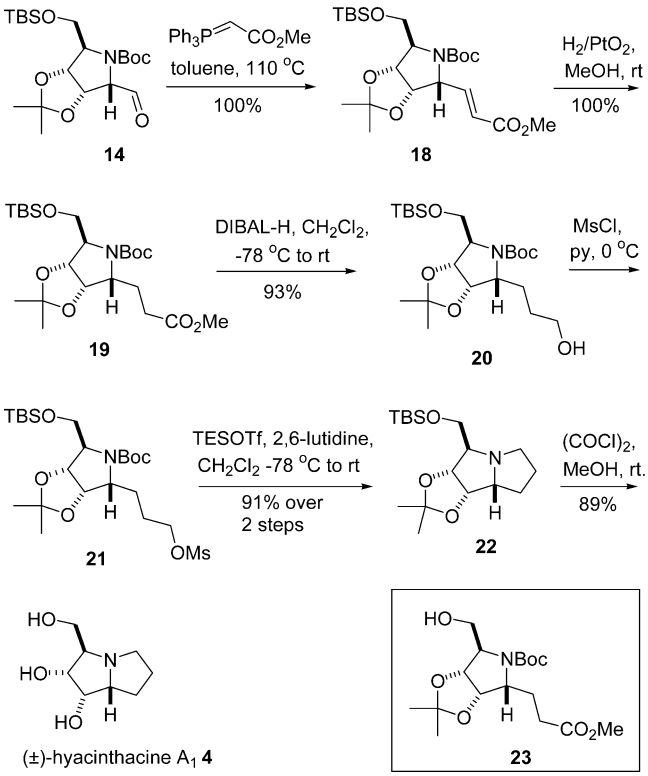
(9) (a) Choi, S.; Bruce, I.; Fairbanks, A. J.; Fleet, G. W. J.; Jones, A. H.; Nash, R. J.; Fellows, L. E. *Tetrahedron Lett.* **1991**, *32*, 5517. (b) Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553. (c) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276. (d) Donohoe, T. J.; Sintim, H. O. *Org. Lett*. **2004**, *6*, 2003. (e) Tang, M.; Pyne, S. G. *Tetrahedron* **2004**, *60*, 5759.

(10) Poli, G. *Tetrahedron Lett.* **1989**, *30*, 7385.

(11) (a) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* **2001**, *57*, 2109. (b) Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron Lett.* **2000**, *41*, 5711.

(12) Trost, B. M.; Crawley, L. M. *J. Am. Chem. Soc.* **2002**, *124*, 9328.

SCHEME 5



yield after filtering the reaction mixture through Celite and evaporating the solvent. The crude product was pure by NMR without the need for purification by column chromatography. Reduction of the ester functionality in **19** to a primary alcohol was required next and so reaction of compound **19** with DIBAL-H in dichloromethane gave alcohol **20** (93%). The use of 2.1 equiv of DIBAL-H in the reaction was key to obtaining a high yield in this reduction as use of a greater excess of reducing agent resulted in inferior yields. Also, addition of ethyl acetate to the reaction mixture, after it had been quenched with aqueous NH_4Cl, was found to be beneficial. We rationalize that the ethyl acetate helps to chelate the aluminum metal byproducts and frees the product from entrapment in the resulting gel. In runs where ethyl acetate was not added, yields as low as 20% were sometimes obtained. With compound **20** in hand, the stage was set for completion of the synthesis.

Next, we chose to activate the primary hydroxyl group by reaction of **20** with methanesulfonyl chloride: this proceeded smoothly (**21**) and was followed by removal of the Boc protecting group with TESOTf/2,6-lutidine which afforded bicycle **22** directly: clearly, the OMs group was proven to be stable to N-deprotection conditions and ring closure took place immediately after the Boc group was removed. We have previously communicated that, for acid sensitive substrates such as **21**, the use of silyl triflates to remove Boc groups on nitrogen is much better than using TFA.[9c] Global deprotection of bicycle **22** with HCl/MeOH gave racemic hyacinthacine A_1 **4** after neutralization with aqueous NaOH and column chromatography eluting with saturated ammonia/methanol/chloroform.

Unfortunately, the NMR of the synthetic compound **4** was different from that reported in the literature.[7] The NMR resonances of the synthetic sample were broader than the natural product and this was attributed to the nitrogen in **4** still being protonated: we did not consider that the difference in enantiopurity between synthetic and natural material was responsible for the discrepancy. At this point the synthetic material was analyzed by the workers who originally isolated the natural product. Increasing the pH of the NMR sample to 9.3 gave sharper resonances but the NMR (chemical shift) of the synthetic compound did not completely match that of the natural product (see Table 1, synthetic versus natural[13]). It was plausible that synthetic hyacinthacine had picked up metal ions during silica column chromatography and that a metal contaminant was responsible for the discrepancy observed in the NMR. In fact it has been reported before that products can be contaminated with potassium cations picked up from commercial silica gel.[14] Therefore, compound **4** was repurified on an ion exchange column (IR-120 H^+ form) eluting with 1 M NH_4OH and the NMR spectrum of the synthetic material was a much better match to the natural product (see Table 1, ion exchange). Previous studies by Wormald and co-workers on samples of 1-epiaustraline had noted chemical shift differences between different samples of the same compound.[15] These researchers concluded that variation in solvent (ionic strength, hydrogen bonding, metal ions) was responsible for these discrepancies but noted that the coupling constants were very similar whatever the chemical shift.

Note that in this case, the multiplicities and coupling constants are the same for natural product, synthetic product before ion exchange, and synthetic product after ion exchange (see Table 1). Moreover, the chemical shift (δ) discrepancy between the natural product and the synthetic product before ion exchange was more pronounced at H-7a, which suggests that a metal or proton was chelated to the nitrogen before ion exchange.

In another experiment, the crude (synthetic) hyacinthacine A_1 was purified on Dowex ion exchange without an initial purification on silica. The NMR of the resulting product in D_2O at neutral pH (see the Supporting Information) was a much closer match to that at pH 9.3. The synthetic material was also analyzed by GCMS and showed an identical match in both retention time and fragmentation pattern to an authentic sample of the natural product. Taking all this evidence in total we conclude that the synthetic material is indeed hyacinthacine A_1 and can confirm the structure of this compound.

One of the lessons learned in this project is that one has to be careful when purifying polyhydroxylated amino compounds as it is easy to contaminate samples with metals due to the compounds exceptional chelating ability.

Synthesis of 1-Epiaustraline from Pyrrole 7. Our second target was 1-epiaustraline, which we envisioned could be prepared by a route similar to that described above, utilizing aldehyde **14** as a common intermediate. In this case, two possible modes of ring closure were envisaged: (i) iodocyclization of a pendant alkene (see

(13) Note that this is the first time that the data for hyacinthacine A1 have been reported in D_2O.

(14) Perepichka, D. F.; Bryce, M. R.; Batsanov, A. S.; McInnes, E. J. L.; Zhao, J. P.; Farley, R. D. *Chem. Eur. J.* **2002**, *8*, 4656.

(15) Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2549.

TABLE 1. NMR Data for Hyacinthacine A_1: Solvent D_2O Referenced to Sodium 3-(Trimethylsilyl)propionate (TSP) at 0.0 ppm, pH 9.3[a]

	^{1}H NMR					^{13}C NMR			
label	natural	synthetic	ion exchange	multiplicity	$^3J_{HH}$ (Hz)	natural	synthetic	ion exchange	
5	3.14	3.37	3.21	m		55.77	55.68	55.73	CH_2
	2.65	2.94	2.73	m					
6	1.98	2.12	2.02	m		27.16	26.74	27.00	CH_2
	1.79	1.93	1.83	m					
7	1.98	2.12	2.02	m		23.87	23.79	23.84	CH_2
	1.79	1.93	1.83	m					
7a	3.59	3.94	3.68	m		65.88	67.59	66.45	CH
1	4.06	4.18	4.09	t	3.8	71.55	70.80	71.29	CH
2	4.01	4.13	4.04	dd	3.8/10.1	75.14	73.62	74.61	CH
3	2.89	3.15	2.97	ddd	3.8/5.7/3.2	69.00	68.87	68.95	CH
8	3.85	3.95	3.87	dd	12.0/3.2	62.88	60.01	61.89	CH_2
	3.68	3.79	3.70	dd	12.0/5.7				

[a] *J* values were the same for all three samples.

TABLE 2. Diastereoselective Addition of a Vinyl Group to Aldehyde 14

entry	reagent	temp (°C)	conversion (%)	**28:29**
1	vinyllithium	−78	100	20:80[a]
2	vinyllithium/DMPU	−78	100	9:91[b]
3	vinylmagnesium bromide	−78	100	40:54[a]
4	vinyltitanium triisopropoxide	−78	29	100:0[b]
5	vinylmagnesium bromide	rt	100	91:8[a]
6	vinylmagnesium bromide + $EuCl_2$	−78	60	84:16[b]
7	vinylmagnesium bromide + CuCl	−78	66	84:16[a]
8	vinylmagnesium bromide + $CoCl_2$	−78	66	84:16[a]

[a] Isolated yields. [b] Determined from ^{1}H NMR of crude product.

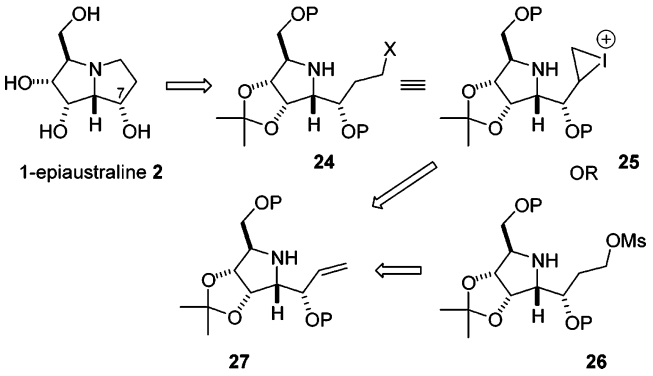
25) and (ii) internal displacement of a leaving group derived from a primary alcohol (see **26**). Both of these routes could start from a common precursor (**27**).

Optimization of Vinymetal Addition to Aldehyde 14. The challenges that were anticipated for this synthesis centered around the addition of vinylmetals to aldehyde **14**, which must be diastereoselective.

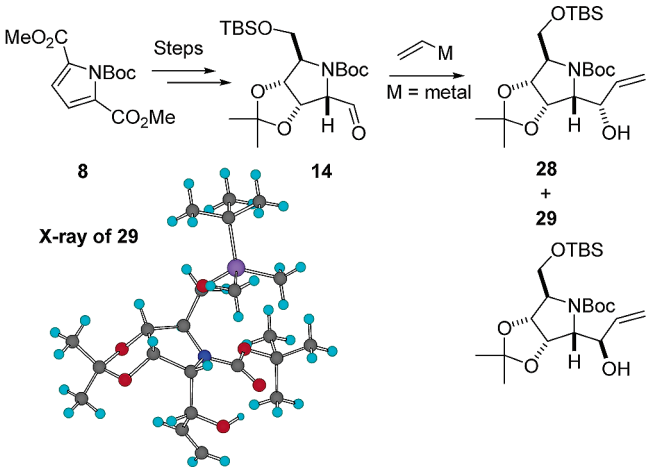
In the event, addition of vinylmetals to aldehyde **14** exhibited interesting and useful characteristics, Table 2.[16] Vinyllithium addition at −78 °C gave the expected Felkin−Ahn product **29** (unwanted for 1-epiaustraline) as the major adduct (Table 2, entry 1); removing all vesitiges of chelation by the addition of DMPU increased this ratio to a synthetically useful 91:9 selectivity (Table 2, entry 2). Swapping to vinylmagnesium bromide at −78 °C also gave the Felkin−Ahn product as the major adduct albeit with a lower selectivity (entry 3). These observations were in accordance with the general trend observed when changing the metal from the less chelating lithium to the more chelating magnesium. Vinyltitanium triisopropoxide (generated by the transmetalation of vinylmagnesium bromide with $ClTi(O^iPr)_3$) gave complete (NBoc) chelation controlled selectivity but the reaction could not be pushed to completion (entry 4). However, addition of vinylmagnesium bromide to **14** *at room temperature* gave a 91:8 mixture of **28**:**29** (compare 40:54 of **28**:**29** at −78 °C). The relative stereochemistry of

(16) For a review see: Mengel, A.; Reiser, O. *Chem. Rev.* **1999**, *99*, 1191.

SCHEME 6. Retrosynthetic Analysis of 1-Epiaustraline



SCHEME 7



28 and **29** was determined by X-ray crystal analysis of **29** (Scheme 7).

A range of Lewis acids such as $EuCl_2$, CuCl, and $CoCl_2$ were also screened as additives for diastereoselection in the addition. Conversions in the 60% range were observed and were coupled to a 84:16 diastereoselectivity (in favor of the chelation-controlled product **28**), irrespective of Lewis acid used (compare entries 3, 6, 7, and 8). Comparison of Table 2 entry 2 with entry 5 shows that our aim of a flexible synthesis is furthered by this study because we can now control the (C-6) stereochemistry at will in these systems.

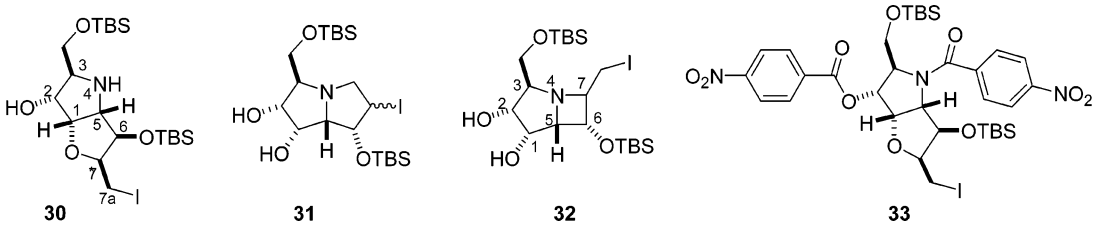
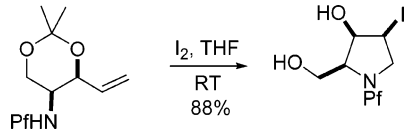


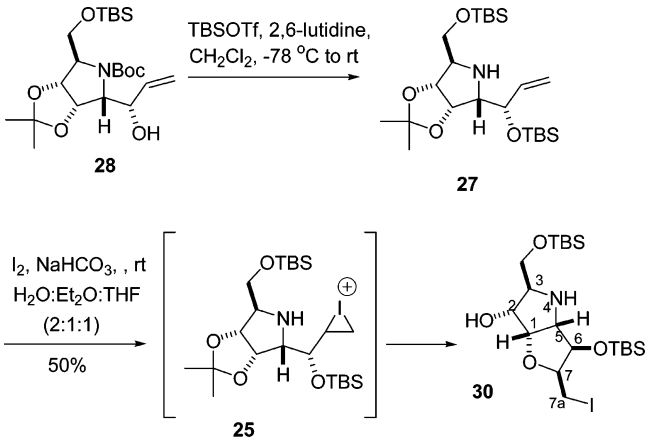
FIGURE 2. Possible structures from iodocyclization of **27**.

SCHEME 8 [a]



[a] Pf = 9-phenylfluoren-9-yl.

SCHEME 9

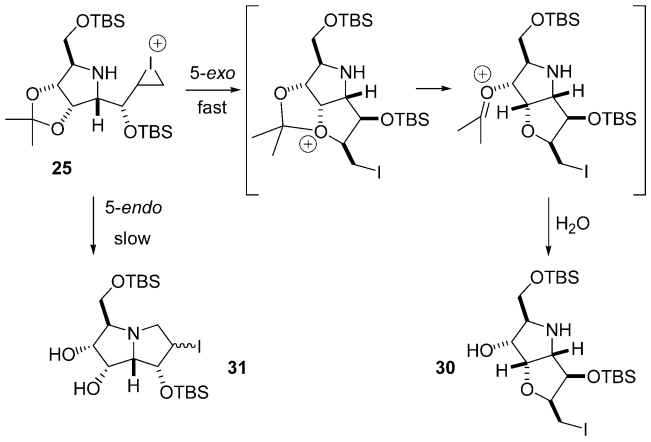


Iodocyclization as a Route toward Pyrrolizidines. There are several reports in the literature documenting the 5-endo iodocyclization of homoallylamines to furnish pyrrolidines (Scheme 8).[17] It was envisioned that the 5-endo iodocyclization of amine **27** would give bicycle **31** (see Figure 2) that could be easily elaborated into 1-epiaustraline or its C6 analogues.

Therefore, we proceeded by deprotecting the Boc group of **28** with TBSOTf/2,6-lutidine (Scheme 9) and simultaneously protecting the allylic alcohol to give **27**. However, subjecting homoallylamine **27** to reaction with iodine and $NaHCO_3$ afforded a product that was clearly not bicycle **31** but one assigned as compound **30** (see Scheme 10 for a plausible mechanism of formation). Though several attempts to get a crystal of **30** (or a derivative) for X-ray crystal analysis failed, detailed spectroscopic evidence showed that the product was most probably **30** with the structure shown.

Consideration of a likely mechanism for the cyclization reaction (i.e., reaction of intermediate **25**) raised three probable structures for the product, **30**−**32**, Figure 2. A ^{13}C APT/DEPT experiment showed that there were two CH_2 carbons in the structure and one of these CH_2 carbons was attached to iodine (RCH_2I: $\delta_C(C_6D_6) = 1.67$ ppm and $\delta_H = 3.28$ and 3.35 ppm). Therefore structure **31** was readily eliminated from the list of potential products as it must have a CH_2−N unit. If adduct **32** (formed via a 4-exo cyclization and then a deprotection of the acetonide ring by $I_2/NaHCO_3$) was the product obtained, then there should exist an HMBC correlation between C3 and H7 or C7 and H3; however, no such HMBC correlation between C3 and H7 or C7 and H3 was observed.

SCHEME 10

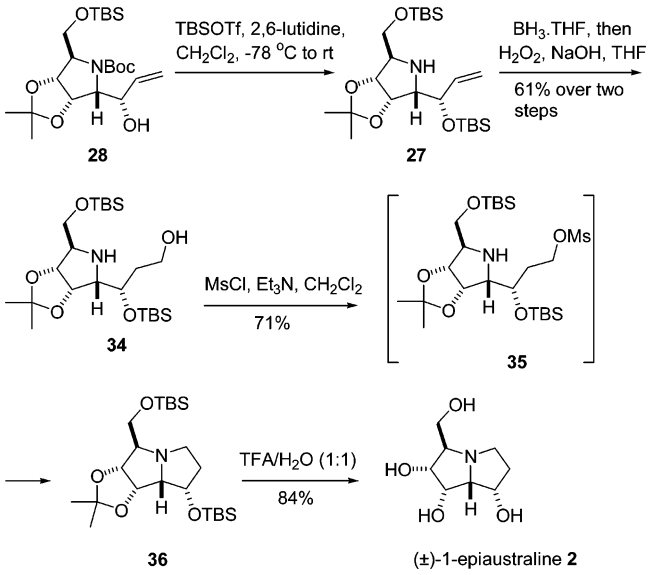


Crucially, perbenzoylation of compound **32** should lead to a compound with two ester functionalities while perbenzoylation of compound **30** would afford a derivative with both an ester and an amide functionality. Subjecting the unknown compound to reaction with excess *p*-nitrobenzoyl chloride and triethylamine led to compound **33** (Figure 2) that showed two different C=O environments (δ = 169.6 and 163.8 ppm) in the product. Moreover, IR evidence also supports our assignment: IR stretches of 1735 (ester functionality) and 1652 cm^{-1} (amide) supported the assignment of structure **33**. This evidence, taken in total, supports structure **30** and implies that the kinetic advantage of 5-*exo* cyclizations over 5-*endo* cyclizations far outweighs the chemoselective preference of nitrogen over oxygen as a nucleophile in ring opening of strained rings (Scheme 10). Moreover, the in situ deprotection of the acetonide unit is also explained by this mechanism.

Ring Closure via Mesylate Intermediates. Given the failure of the iodocyclization route, we reverted to the tactics which worked well for hyacinthacine A_1 and examined the internal (OMs) displacement route. The challenges here revolve around regioselective hydroboration of the terminal alkene within **28** together with the order of events regarding *N*-Boc deprotection and oxygen activation. Starting from **28** it made sense to deprotect the Boc group at the same time as placing a silyl group

(17) (a) Jones, A. D.; Knight, D. W.; Hibbs, D. E. *J. Chem. Soc., Perkin Trans 1*. **2001**, 1182. (b) Lee, W. S.; Jang, K. C.; Kim, J. H.; Park, K. H. *Chem. Commun.* **1999**, *3*, 251. (c) Wilson, S. R.; Sawicki, R. A. *J. Org.* Chem. **1979**, *44*, 287.

SCHEME 11



on the secondary hydroxyl: this sequence would cut one step from the total provided that the ring closure could be effected from an amino alcohol.

Therefore, we proceeded from **28** by reaction with TBSOTf (*N*-Boc deprotection and formation of OTBS) and then hydroboration of **27** proceeded well (3 equiv of BH_3), with an oxidative workup employed to produce alcohol **34** with good regioselectivity (>7:1, Scheme 11). Subsequent mesylation of **34** was chemoselective (primary alcohol mesylated in the presence of the hindered secondary amine) and, indeed, mesylate **35** could not be isolated as cyclization ensued rapidly to afford bicycle **36**. Global deprotection of **36** with TFA afforded (±)-epiaustraline **2** in 84% yield. The NMR of the synthetic compound matched exactly that of the natural product. Curiously, though 1-epiaustraline was purified on silica, the problems associated with hyacinthacine contamination on silica were not encountered here.

Conclusion

Total syntheses of two natural products have been accomplished starting from inexpensive *N*-Boc-pyrrole. Hyacinthacine A_1 was prepared for the first time in a laboratory (13 steps, 31% overall yield) and an efficient route to 1-epiaustraline (12 steps, 14% overall yield) was also discovered. Two different approaches to construction of the 5,5-bicyclo ring system were investigated and it was discovered that an internal S_N2 type displacement of a mesylate was an effective way of forming the pyrrolizidine ring system. This displacement route has extra flexibility in that ring closure can be accomplished from an amino alcohol precursor that is activated regioselectively (1-epiaustraline). Alternatively, should the situation require that the nitrogen atom remain protected, prior activation of a primary hydroxyl group gave a OMs derivative that was stable to conditions required for N-deprotection (hyacinthacine A_1).

The combination of these tactics for forming the pyrrolizidine ring system together with the stereochemical flexibility eminating from the partial reduction reaction means that a highly versatile route has been uncovered. In total, these syntheses have five steps whereby either diastereoselectivity, chemoselectivity, or regioselectivity was achieved in synthetically useful ratios. Future studies will concentrate on the syntheses of more complex members of this family of natural products and also extend the reduction methodology to produce enantiopure compounds.[18]

Experimental Section

4-(*tert*-Butyldimethylsilyloxymethyl)-6-(2-methoxycarbonylvinyl)-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylic Acid *tert*-Butyl Ester (18). To a solution of aldehyde **14** (1.0 g, 2.4 mmol) in dry toluene (30 mL) was added methyl (triphenylphosphoranylidene)acetate (2.4 g, 7.2 mmol) and the mixture was heated at reflux for 24 h. Evaporation of the solvent and column chromatography (10% EtOAc in light petroleum) afforded enone **18** (1.13 g, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.75 (dd, J = 15.8 and 8.4 Hz, 1H), 5.76 (d, J = 15.8 Hz, 1H), 4.67 (m, 1H), 4.61 (d, J = 5.9 Hz, 1H), 4.43 and 4.34 (t × 2, J = 7.5 Hz, 1H), 4.10−3.83 (m, 2H), 3.70−3.54 (m, 4H), 1.41 (s, 3H), 1.39 and 1.32 (s × 2, 9H), 1.25 (s, 3H), 0.83 (s, 9H), −0.01 (s, 3H), and −0.02 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5, 153.9, 148.1, 120.2, 111.6, 81.8, 77.4, 64.1, 63.8, 62.1, 51.3, 28.1, 25.8, 24.7, 18.0, −5.6, and −5.7. IR (film) 2954, 2859, 1727, 1697, 1472 cm^{-1}. HRMS (ES) found [M + H$^+$] 472.273067, $C_{23}H_{42}NO_7Si$ requires 472.273067.

4-(*tert*-Butyldimethylsilyloxymethyl)-6-(2-methoxycarbonylethyl)-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylic Acid *tert*-Butyl Ester (19). Alkene **18** (1.1 g, 2.33 mmol) was stirred in methanol (20 mL) and PtO_2 (52.2 mg, 0.23 mmol) under H_2 at atmospheric pressure and room temperature for 3 h. The reaction mixture was filtered through Celite and the solvent evaporated to afford compound **19** (1.1 g, 100%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.63 (t, J = 6.3 Hz, 1H), 4.58 (t, J = 6.3 Hz, 1H), 4.13 and 3.60 (m × 2, 1H), 4.00 and 3.9 (m × 2, 1H), 3.79 and 3.52 (m × 2, 1H), 3.70 (m, 1H), 3.60 (s, 3H), 2.65, 2.43 and 2.27 (m × 3, 3H), 1.91 (m, 1H), 1.45 (s, 3H), 1.41 (br s, 9H), 1.29 (s, 3H), 0.83 (s, 9H), −0.01 (s, 3H), and −0.02 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.9, 154.4, 110.9, 81.7, 81.4, 80.4, 80.0, 79.7, 79.5, 64.3, 63.5, 62.1, 61.9, 61.6, 51.3, 30.9, 28.4, 25.8, 24.7, 18.0, −5.6, and −5.7. IR (film) 2955, 2859, 1742, 1695, 1473 cm^{-1}. HRMS (ES) found [M + H$^+$] 474.2882, $C_{23}H_{44}NO_7Si$ requires 474.2887.

4-(*tert*-Butyldimethylsilyloxymethyl)-6-(3-hydroxypropyl)-2,2-dimethyltetrahydro[1,3]dioxolo[4,5-*c*]pyrrole-5-carboxylic Acid *tert*-Butyl Ester (20). To a solution of ester **19** (1.0 g, 2.11 mmol) in dichloromethane (25 mL) at −78 °C was slowly added DIBAL-H (3.0 mL of 1.5 M in toluene, 4.5 mmol) over 10 min. The mixture was stirred at −78 °C and then slowly warmed to room temperature overnight after which MeOH (1 mL) was slowly added. Saturated aq NH_4Cl (3 mL) was added followed by EtOAc (50 mL). The mixture was stirred for 30 min and the resulting gel was filtered through a pad of Celite and the Celite was washed several times with EtOAc. The filtrate was evaporated under reduced pressure and the product was purified by flash column chromatography (eluting with 10−20% EtOAc in light petroleum) to afford **20** (874 mg, 93%) as a clear oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.70 (t, J = 6.2 Hz, 1H), 4.64 (d, J = 6.2 Hz, 1H), 4.16 and 3.87 (m × 2, 1H), 3.99 and 3.93 (m × 2, 1H), 3.87−3.40 (m, 4H), 2.35 (m, 1H), 2.20 (m, 1H), 1.81−1.52 (m, 2H), 1.51 (s, 3H), 1.44 (s, 9H), 1.35 (s, 3H), 0.90 (s, 9H), 0.04 (s, 3H), and 0.03 (s, 3H). NB: most multiplets are broad in

(18) We have already developed a method for producing *trans*-**10** in enantiopure form directly from the partial reduction reaction of **3**: Donohoe, T. J.; Headley, C. E.; Rigby, C. L.; Freestone, G. C.; Cousins, R. P. C.; Bhlay, G. *Org. Lett.* **2004**, *6*, 3055. Further work is ongoing to understand and optimize this sequence.

nature, suggesting different conformers in equilibrium. ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.8, 110.0, 81.1, 79.0, 78.7, 63.7, 62.7, 61.9, 61.4, 27.6, 25.0, 24.0, 17.2, −6.3, and −6.5. IR (film) 3462 (OH), 2932 (CH), 1688 (C=O), and 1473 cm^{-1}. HRMS (ES) found $[M + H^+]$ 446.2924, $C_{22}H_{44}NO_6Si$ requires 446.2938.

4-(*tert*-Butyldimethylsilyloxymethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*a*]pyrrolizine (22). (a) To a solution of alcohol **20** (810 mg, 1.82 mmol) in dry pyridine (5 mL) at 0 °C was added $MeSO_2Cl$ (341 mg, 3 mmol). The mixture was stirred at 0 °C for 10 min and then warmed to room temperature. Stirring was continued for a further 1 h and the solvent was evaporated under reduced pressure. The residue was redissolved in EtOAc (50 mL). The organic layer was washed with water (10 mL × 2). The organic layer was dried ($MgSO_4$) and the solvent evaporated under reduced pressure. The crude mesylate was used in the next step without further purification.

(b) To the crude mesylate in dichloromethane (10 mL) at −78 °C was sequentially added 2,6-lutidine (1.0 mL) and TESOTf (1.9 mL). The reaction mixture was slowly warmed to room temperature over 1 h and stirred for 24 h. Saturated aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with EtOAc (40 mL × 3). The organic layer was dried ($MgSO_4$) and evaporated under reduced pressure. The crude product was dry loaded onto silica gel and left to stand for 3 h before being chromatographed (100% $CHCl_3$ to 30% MeOH in $CHCl_3$) to afford bicycle **22** (542 mg, 91% over two steps) as a clear oil. ^1H NMR (400 MHz, $CDCl_3$) δ 4.74 (dd, J = 6.0 and 2.3 Hz, 1H), 4.64 (t, J = 5.7 Hz, 1H), 3.98 (dd, J = 8.2 and 5.3 Hz, 1H), 3.80 (dd, J = 10.7 and 4.9 Hz, 1H), 3.75 (dd, J = 10.7 and 4.9 Hz, 1H), 3.39 (m, 2H), 3.14 (q, J = 7.5 Hz, 1H), 2.25 (m, 1H), 2.02 (m, 3H), 1.51 (s, 3H), 1.33 (s, 3H), 0.91 (s, 9H), and 0.07 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 112.2, 84.9, 81.5, 70.4, 68.4, 64.1, 55.5, 26.7, 25.9, 25.5, 24.2, 23.9, 18.2, −5.5, and −5.7. IR (film) 2932, 1471, and 1381 cm^{-1}. HRMS (ES) found $[M + H^+]$ 328.2317, $C_{17}H_{34}NO_3Si$ requires 328.2308.

Hyacinthacine A_1 (4). To a solution of bicycle **22** (500 mg, 1.53 mmol) in dry MeOH (10 mL) at room temperature was added oxalyl chloride (0.5 mL). The mixture was stirred overnight and the solvent evaporated under reduced pressure. The crude product was purified on Dowex 50X8-100 ion-exchange resin (eluting with 1 M aq NH_4OH) to afford hyacinthacine A_1 (236 mg, 89%) as an oil. ^1H NMR (400 MHz, D_2O) δ 4.03 (t, J = 3.8 Hz, 1H), 4.00 (dd, J = 10.1 and 3.8 Hz, 1H), 3.81 (dd, J = 12.0 and 3.2 Hz, 1H), 3.66 (dd, J = 12.0 and 6.6 Hz, 1H), 3.63 (m, 1H), 3.14 (m, 1H), 2.911 (ddd, J = 6.6, 3.8, and 3.2 Hz, 1H), 2.67 (m, 1H), 1.95 (m, 2H), and 1.77 (m, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 74.6, 71.3, 68.9, 66.4, 62.0, 55.7, 49.2, 27.0, and 23.8.

3-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldimethylsilyloxymethyl)-2-iodomethylhexahydrofuro[3,2-*b*]pyrrol-6-ol (30). To a solution of bis-silyl compound **27** (340 mg, 0.74 mmol) in a 2:1:1 mixture of H_2O:THF:Et_2O (8 mL) was added $NaHCO_3$ (248.7 mg) and iodine (566.1 mg, 2.23 mmol) at room temperature. The mixture was stirred overnight and saturated $Na_2S_3O_7$ was added until the mixture turned colorless. EtOAc (20 mL) was added and the organic layer separated. The aqueous layer was extracted once more with EtOAc (5 mL) and the combined organic layers were dried ($MgSO_4$) and solvent evaporated in vacuo. Purification of the residue (5−10% EtOAc in light petroleum) gave iodide **30** (201 mg, 50%) and recovered starting material **27** (80 mg). ^1H NMR (400 MHz, benzene-d_6) δ 4.62 (t, J = 4.8 Hz, 1H), 4.30 (ddd, J = 8.6, 5.8, and 3.0 Hz, 1H), 4.20 (d, J = 2.0 Hz, 1H), 3.91 (dd, J = 8.6 and 4.5 Hz, 1H), 3.87 (dd, J = 10.6 and 2.8 Hz, 1H), 3.79 (dd, J = 10.4 and 3.3 Hz, 1H), 3.69 (d, J = 4.5 Hz, 1H), 3.35 (dd, J = 9.3 and 8.3 Hz, 1H), 3.28 (dd, J = 9.3 and 5.6 Hz, 1H), 2.79 (dt, J = 8.6 Hz, 1H), 2.46 (br s, 1H), 1.02 (s, 9H), 0.99 (s, 9H), 0.18 (s, 3H), 0.14 (s, 6H), and 0.07 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 84.8, 83.9, 80.0, 74.9, 68.2, 65.2, 62.2, 26.3, 26.1, 18.8, 18.3, 1.67, −4.2, −4.4, −5.1, and −5.2. IR (film) 3300, 3125, 2925, and 1470 cm^{-1}. HRMS (ES) found $[M + H^+]$ 544.1782, $C_{20}H_{43}NO_4Si_2I$ requires 544.1775.

4-Nitrobenzoic Acid 3-(*tert*-Butyldimethylsilyloxy)-5-(*tert*-butyldimethylsilyloxymethyl)-2-iodomethyl-4-(4-nitrobenzoyl)hexahydrofuro[3,2-*b*]pyrrol-6-yl Ester (33). To the cyclization product **30** (50 mg, 0.09 mmol) in CH_2Cl_2 (2 mL) were added DMAP (cat.), *p*-nitrobenzoyl chloride (51.2 mg, 0.28 mmol), and distilled triethylamine (0.1 mL) and the mixture was stirred for 48 h. The reaction mixture was poured into water (5 mL) and then extracted with EtOAc (3 × 10 mL), dried (Na_2SO_4), filtered, and evaporated under reduced pressure. The product was purified by flash column chromatography (eluting with 5% EtOAc in light petroleum) to afford compound **33** (32 mg). ^1H NMR (400 MHz, $CHCl_3$) δ 8.30 (m, 6H), 7.76 (d, J = 8.6 Hz, 2H), 5.45 (m, 1H), 5.10 (t, J = 6.1 Hz, 1H), 4.67 (d, J = 1.5 Hz, 1H), 4.63 (d, J = 5.8 Hz, 1H), 4.38−4.20 (m, 2H), 3.50 (d, J = 10.9 Hz, 1H), 3.17 (m, 3H), 0.91 (s, 9H), 0.87 (s, 9H), 0.34 (s, 3H), 0.20 (s, 3H), −0.02 (s, 3H), and −0.04 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 163.8, 150.8, 149.1, 141.9, 134.7, 131.0, 128.6, 124.1, 123.7, 84.7, 78.8, 74.8, 72.1, 66.4,63.4, 25.8, 25.7, 18.0, 0.97, 0.18, −4.2, −5.2, −5.7, and −5.8. IR (film) 2956, 2858, 1735, 1652, 1603, 1527, and 1471 cm^{-1}. CIMS *m/z* (rel intensity) 842 (55%, MH^+), 784 (100), 754 (15), and 710 (15).

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Supporting Information Available: Detailed procedures and spectroscopic data for compounds **2**, **8**, *trans*-**10**, **14**, **15**, **16**, **17**, **28**, and **34**. This material is available free of charge via the Internet at http://pubs.acs.org.

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