ORGANIC LETTERS

2004
Vol. 6, No. 12
2003−2006

A Concise Total Synthesis of (±)-1-Epiaustraline

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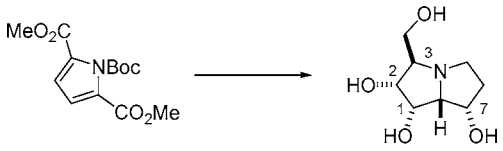
Received April 1, 2004

ABSTRACT



7 1-epiaustraline **3**

A concise total synthesis of 1-epiaustraline 3 is described that utilizes a diastereoselective Birch reduction of an electron-deficient pyrrole and a chelation-controlled vinyl Grignard addition to an aldehyde to introduce the C7 stereocenter. The C1 and C2 stereocenters were set through an OsO_4-catalyzed dihydroxylation.

Glycosidases are involved in the degradation of carbohydrates[1] and the processing of glycoproteins[2] and glycolipids[3] in both eukaryotic and prokaryotic cells. These glyco-molecules are important for energy production, cell wall fortification, cell recognition, and other key processes.[4] The need to regulate glyco-molecules is therefore indispensable to the cell. This central role of glycosidases makes them an attractive target for drug discovery programs.[5] Fleet and co-workers have indicated that glycosidase inhibitors such as (+)-swainsonine and its analogues are potential therapeutic agents for the treatment of tuberculosis.[6] Other glycosidase inhibitors such as castanospermine[7] and deoxynojirimycin[8] have found use in anticancer and antiretroviral research.[9]

The discovery of the alexines[10] and australines[11] (also potent inhibitors of various glycosidases) has prompted a spate of research into the synthesis of these structurally interrelated polyhydroxylated pyrrolizidines and also analogues thereof.[12] The mode of inhibition of these pyrrolizidines is postulated to arise from their highly oxygenated structures and the ability of the protonated pyrrolizidine derivative to bind as a transition state analogue.[13]

1-Epiaustraline **3** (Figure 1) is a polyhydroxylated pyrrolizidine produced by the plant *Castanospermum Australae* (commonly known as the Moreton Bay Chestnut). Both Fleet[14] and Harris[15] independently reported its isolation and structural elucidation. It has been tested for glycosidase inhibition and found to inhibit α-glucosidase amyloglucosidase (50% inhibition at 26 μM), glucosidase I, β-glucosidase,

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10.1021/ol049397s CCC: $27.50
Published on Web 05/15/2004

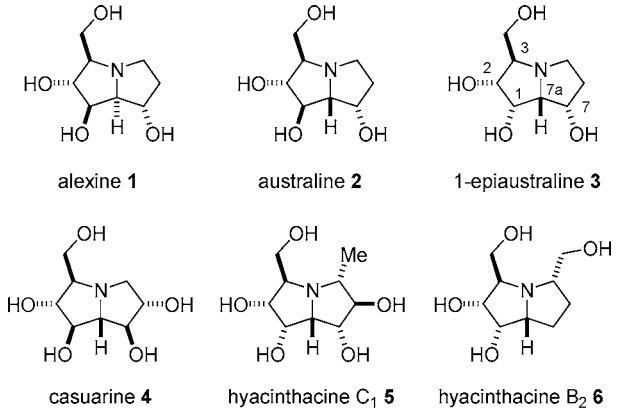
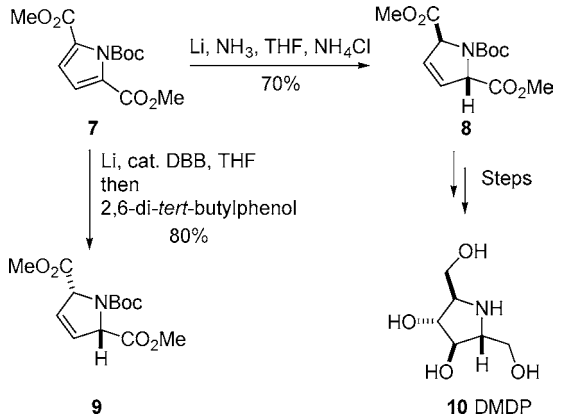


Figure 1. Naturally occurring polyhydroxylated pyrrolizidines.

and α-mannosidase at millimolar levels. 1-Epiaustraline **3** also inhibits yeast α-glucosidase (50% inhibition at 270 μM), an activity not demonstrated by other α-glucosidase inhibitors.[14,15] There are only three reported syntheses of 1-epiaustraline by Fleet,[16] Ikota,[17] and Denmark.[18] Fleet's synthesis involves the manipulation of a mannose derivative in 14 steps and 7.2% overall yield. Ikota's synthesis started from a glutamine derivative and proceeded in 15 steps and 4.7% overall yield. Denmark utilized a tandem intramolecular [4 + 2]/intermolecular [3 + 2] nitroalkene cycloaddition as key steps to access 1-epiaustraline **3** in 11 steps and 7.0% overall yield. We were interested in the synthesis of **3**, as we believed that a modular approach to the construction of **3** would in principle allow later syntheses of the more hydroxylated analogues such as hyacinthacine C_1 **5** and casuarine **4**.

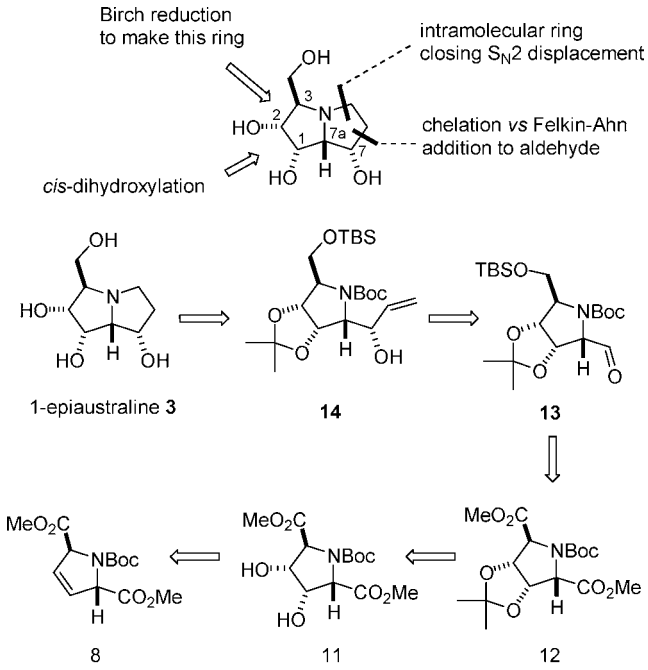
In our earlier paper, we demonstrated flexibility in the partial reduction of 2,5-disubstituted pyrroles and the application of this reaction to the synthesis of (2*RS*,5*RS*)-bis-(hydroxymethyl)-3(*RS*),4(*RS*)-dihydroxypyrrolidine (DMDP) (Scheme 1). [19] Herein, we report a further extension of this

Scheme 1



novel methodology to prepare the more functionalized polyhydroxylated pyrrolizidine **3**. Our retrosynthetic analysis of 1-epiaustraline **3** is shown in Scheme 2.

Scheme 2



The key retrosynthetic steps involved closure to the 5,5-ring system by an intramolecular S_N2-type displacement on a derivative of **14**. The route would also involve a chelation-controlled vinyl anion addition to aldehyde **13**, which would itself be prepared from compound **12** by reduction. The *cis*-diol unit within **12** would be made by dihydroxylation of **8** (via **11**), and it was known that compound **8** could be easily prepared from pyrrole **7**.[19]

Therefore, our synthesis of the aldehyde **13** began with pyrrole **7**, which was prepared in one step and 76% yield from *N*-Boc pyrrole, lithium tetramethylpiperidine, and methyl chloroformate in THF.[19] Subjecting **7** to the reductive Birch conditions (Li in NH_3/THF) and quenching the reaction with saturated aqueous NH_4Cl gave the reduced product (±)-**8** (greater than 6:1 diastereoselectivity) in multigram quantities (Scheme 3).

Exposure of the diester **8** to standard Poli dihydroxylation conditions (cat. OsO_4, Me_3NO [3 equiv] in CH_2Cl_2)[20] gave the diol **11** as a single diastereoisomer in an excellent yield of 95%. Compound **11** was quite stable and could be chromatographed on silica gel and stored at room temperature for months without any detectable decomposition. Simple acetonide protection of diol **11**, following a standard procedure, gave acetonide **12** in 94% yield (Scheme 3).

To access the correct regioisomer **15**, we needed to distinguish between the two ester functionalities within acetonide **12**. Pleasingly, a methanolic solution of $NaBH_4$

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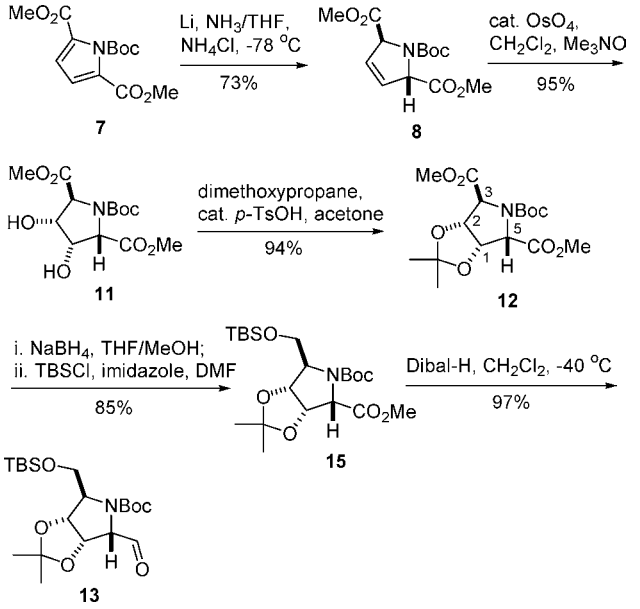
Scheme 3



reduced the C3 ester of **12** to afford **15** after TBS protection. The observed regioselectivity was anticipated because the C5 ester functionality in **12** was more sterically hindered as a result of its *cis* relationship to the acetonide unit. After extensive experimentation, aldehyde **13** was obtained after a DIBALH reduction of **15** at −40 °C. Performing the reaction at lower temperatures such as −78 °C returned starting material quantitatively, whereas increasing the temperature above −40 °C resulted in over-reduction of the ester functionality into an alcohol.

We then proceeded to examine the addition of vinylmetals to aldehyde **13** (Scheme 4). Many of these reactions exhibited interesting characteristics. Vinyllithium addition at −78 °C gave the expected Felkin-Ahn product **16** as the major adduct. Changing to vinylmagnesium bromide at −78 °C still gave the Felkin−Ahn product as the major adduct albeit with a lower selectivity. These observations were in accordance with the general trend observed with changing the metal from the less chelating lithium to the more chelating magnesium (Scheme 4). Vinyltitanium triisopropoxide (generated by the transmetalation of vinylmagnesium bromide with $ClTi(O^iPr)_3$) gave complete chelation-controlled selectivity for **14**, but the reaction could not be pushed to completion. However, adding vinylmagnesium bromide to **13** at room temperature gave a 91:8 mixture of **14**:**16** (compare 40:54 of **14**:**16** at −78 °C). Thus, we have found two sets of procedures that give either **14** or **16** selectively.

The relative stereochemistry of **14** was deduced from a crystal structure of the compound **16**. With **14** in hand, we proceeded by deprotecting the Boc group and simultaneously protecting the hydroxyl functionality with TBSOTf and 2,6-lutidine in CH_2Cl_2 (Scheme 5).[21] This nontraditional deblocking agent was crucial as the use of strong acids to take

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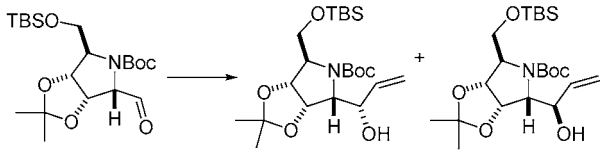
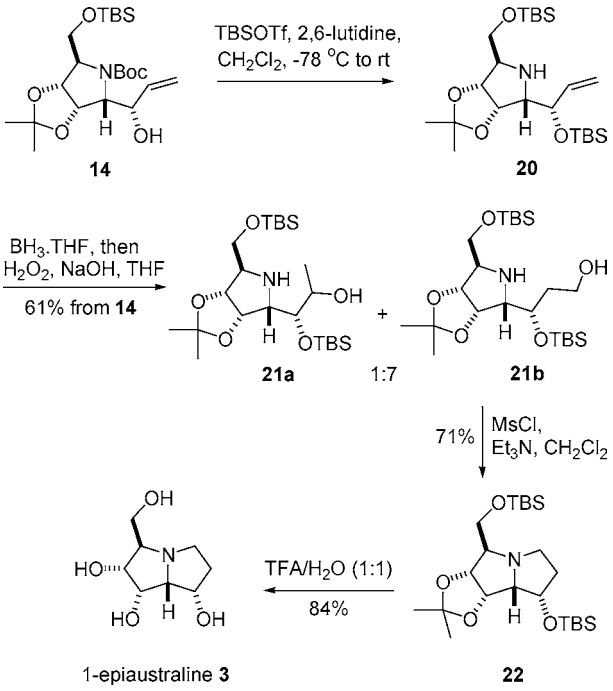
Scheme 4



reagent	temp. °C	conversion (%)	**14:16**[a]
vinyllithium	−78	100	20:80
vinyllithium/ DMPU	−78	100	9:91[b]
vinylmagnesium bromide	−78	100	40:54
vinylmagnesium bromide	rt	100	91:8
vinyltitanium triisopropoxide	−78	29	100:0[b]

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

Scheme 5



off the Boc group partially deprotected the TBS and acetonide functionalities in **14**.

The end-game was executed in a straightforward fashion. Regioselective borane-mediated addition across the alkene gave a 7:1 regioisomeric mixture of **21b** and **21a** that could not be separated by column chromatography. At least 2 equiv of BH_3.THF was needed for complete reaction as the first equivalent of BH_3.THF reacted with the secondary amine to form an adduct. Reaction of a mixture of **21a** and **21b** with $MeSO_2Cl/Et_3N$ in CH_2Cl_2 gave the cyclized product

22 via a S_N2 displacement of the mesylate formed in situ (Scheme 5). An operationally simple global deprotection of **22** with aqueous TFA at room temperature afforded (±)-epiaustraline **3** in 84% yield. This synthetic material exhibited spectroscopic data that matched that of the natural product.[18]

To conclude, we have shown the effectiveness of partial reduction of electron-deficient pyrroles by completing a 12-step synthesis of (±)-1-epiaustraline **3** in 14% overall yield. The flexibility in our approach to access this biologically active molecule is noteworthy, and we are currently utilizing this flexibility to synthesize other structurally related polyhydroxylated pyrrolizidines. Moreover, a recently developed route to enantioenriched **8** should in principle allow the preparation of enantioenriched 1-epiaustraline **3** following the aforementioned synthetic approach.[22]

Acknowledgment. We thank the Leverhulme Trust for funding this project. We also thank Dr. Andrew Cowley for performing X-ray crystal analysis on **16**. Pfizer, AstraZeneca, and Novartis are thanked for unrestricted funding. We thank Professor S. E. Denmark for providing NMR spectra of natural and synthetic epiaustraline.

Supporting Information Available: Experimental procedures and analytical and spectroscopical characterization of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL049397S

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