ORGANIC LETTERS

2008
Vol. 10, No. 16
3615−3618

Flexible Strategy for the Synthesis of Pyrrolizidine Alkaloids

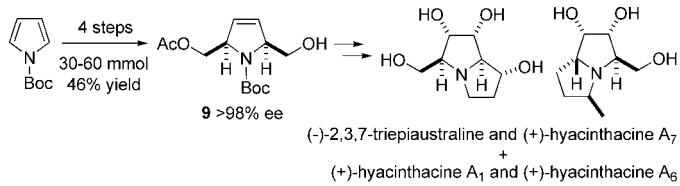
Timothy J. Donohoe,*,† Rhian E. Thomas,† Matthew D. Cheeseman,† Caroline L. Rigby,† Gurdip Bhalay,§ and Ian D. Linney‡

Department of Chemistry, University of Oxford, Chemistry Research Laboratory, Mansfield Road, Oxford, OX1 3TA, United Kingdom, The James Black Foundation, 68 Half Moon Lane, Dulwich, London, SE24 9JE, United Kingdom, and Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex, RH12 5AB, United Kingdom

timothy.donohoe@chem.ox.ac.uk

Received June 23, 2008

ABSTRACT



A general strategy for the production of pyrrolizidine alkaloids is described, starting from intermediate (+)−9. The key features are diastereoselective dihydroxylation, inversion at the ring junction by hydroboration of an enamine, and ring closure to form the bicyclo ring system. This route is attractive because of its brevity and versatility; four natural products were prepared with differing stereochemistry and substitution patterns. Finally, this work allowed assignment of the absolute stereochemistry of 2,3,7-triepiaustraline and hyacinthacine A_7.

In 1988, Fleet et al. reported the isolation of a novel type of polyhydroxylated pyrrolizidine alkaloid from the seedpods of *alexa leiopetala*.[1] The *alexa* species of trees are native to South America, and at the time of publication, no alkaloids had previously been reported to occur in this genus. This compound was a tetrahydroxy pyrrolizidine alkaloid with a unique substitution pattern and was named alexine **1**. While numerous pyrrolizidine alkaloids had previously been isolated bearing carbon substituents at C-1,[2] this was the first example of such a compound bearing a carbon substituent at C-3. Since that time, a large group of polyhydroxylated pyrrolizidines have been isolated from various related plant families (Figure 1), and these structures have proven to be a rich source of glycosidase inhibitors of structural diversity.[3]

Glycosidase inhibitors are worthwhile targets for synthesis and testing since they are currently receiving considerable attention as possible therapeutic agents for treatment of tumor metastasis and viral infections and as antidiabetic agents.[4] Also, novel oral treatment of lysosomal storage diseases

† University of Oxford.
§ Novartis.
‡ The James Black Foundation.

(1) Nash, R. J.; Fellows, L. E.; Dring, J. V.; Fleet, G. W. J; Derome, A. E.; Hamor, T. A.; Scofield, A. M.; Watkin, D. J. *Tetrahedron Lett.* **1988**, *20*, 2487.

(2) (a) Robins, D. J. *Nat. Prod. Rep.* **1987**, *4*, 577. (b) Chamberlin, A. R.; Chung, J. Y. L. *J. Org. Chem.* **1985**, *50*, 4425.

(3) (a) Nash, R. J.; Thomas, P. I.; Waigh, R. D.; Fleet, G. W. J.; Wormald, M. R.; Lilley, P. M.; Watkin, D. J. *Tetrahedron Lett.* **1994**, *35*, 7849. (b) Kato, A.; Kano, E.; Adachi, I.; Molyneux, R. J.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Wormald, M. R.; Kizu, H.; Ikeda, K.; Asano, N. *Tetrahedron Asymmetry* **2003**, *14*, 325. (c) Yamashita, T; Yasuda, K.; Kizu, H.; Kameda, Y.; Watson, A. A.; Nash, R. J.; Fleet, G. W. J.; Asano, N. *J. Nat. Prod.* **2002**, *65*, 1875. (d) 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. (e) Asano, N.; Kuroi, 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.

(4) Asano, N. *Glycobiology* **2003**, *13*, 93R.

(5) (a) Cox, T.; Lachmann, R.; Hollak, C.; Aerts, J.; van Weely, S.; Hrebicek, M.; Platt, F.; Butters, T.; Dwek, R.; Moyses, C.; Gow, I.; Elstein, D.; Zimran, A. *Lancet* **2000**, *355*, 1481. (b) Platt, F. M.; Neises, G. R.; Reinkensmeier, G.; Townsend, M. J.; Perry, V. H.; Proia, R. L.; Winchester, B.; Dwek, R. A.; Butters, T. *Science* **1997**, *276*, 428.

10.1021/ol801415d CCC: $40.75 © 2008 American Chemical Society
Published on Web 07/18/2008

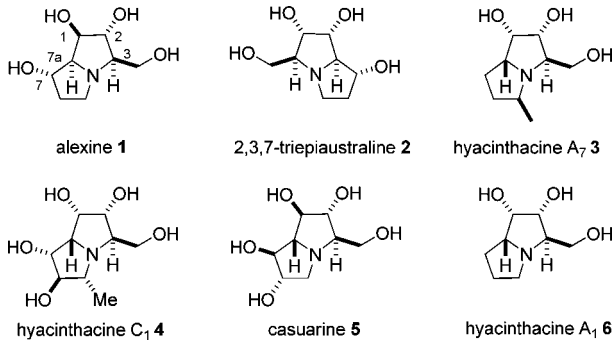


Figure 1. Representative pyrrolizidine alkaloids found in nature.

using specific glycosidase and glycosyltransferase inhibitors are attracting significant interest.[5]

There is considerable structural diversity within the pyrrolizidine alkaloids that have been isolated so far, with wide variations in stereochemistry (cf **1** and **2**) and substitution pattern on the lower five membered ring as drawn (cf **4** and **5**, Figure 1).

Several research groups have been active in this area and have synthesized a variety of both natural and unnatural polyhydroxylated pyrrolizidines containing *cis*-C-1,2 hydroxyl stereochemistry (natural product numbering system).[6]

It is worth pointing out that the absolute configuration is not known for a significant number of these compounds that have so far eluded synthesis.

An ideal approach to these compounds would be one that was both short and efficient and yet allows access to many structures from a defined core synthetic route.

Our synthetic strategy, which we believe fulfils the above requirements, revolved around the transformation of *N*-Boc pyrrole **7** into functionalized enantiopure compound (+)-**9** in just 4 steps and which can be carried out on a multigram scale utilizing both the ammonia free partial reduction of pyrroles (this sets the *cis*-C2,5 stereochemistry within **8**) and an enzymatic desymmetrisation which gives monoacetate **9** of high enantiopurity, Figure 2.[7]

This paper will concentrate on the manipulation of this versatile compound to produce a variety of pyrrolizidine natural products with differing stereochemistry and substitution patterns. The key to our strategy is an ability to dihydroxylate the C3,4 alkene of **9** and then to extend either arm of the resulting molecule by addition to an aldehyde. Another key question arose as to our ability to invert the stereochemistry at either C-2 or C-5 of **9** and hence access the widely distributed *trans* series of natural products. To

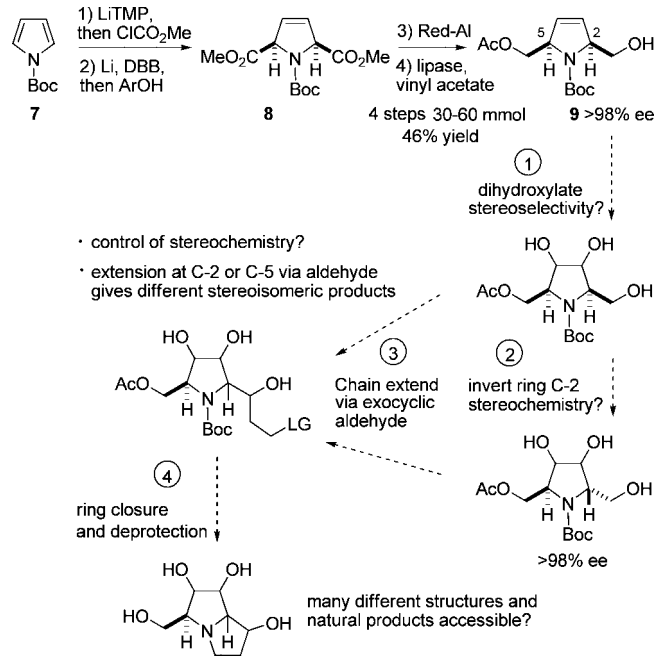


Figure 2. Synthetic analysis.

complete the synthesis. we have chosen either reductive amination or S_N2 displacement as suitable methods for closing the final ring.

The advantage of this strategy is that it is extremely flexible and allows for the preparation of a number of these natural product targets. For the sake of simplicity, a common theme to all of the targets reported in this paper is the *cis* relationship between the C-3,4 hydroxyl groups; studies reporting *trans* configured diols (which can also be accessed) at these positions will be reported later.

To highlight the utility of this compound in synthesis, we chose 2,3,7-triepiaustraline **2**[3b] as a first target, and began with a highly stereoselective (*anti*) *cis*-dihydroxylation of alkene **9** under Poli conditions (>20:1 dr),[8] followed by protection as the corresponding acetonide to yield **10** (82% over two steps), Scheme 1. We then proceeded to oxidize the primary alcohol to an aldehyde with the Dess-Martin periodinane (DMP) and subsequent addition of the Luche allyl-zinc reagent proved to be diastereoselective (>10:1) for the Felkin Ahn stereoisomer **11**.[9] Following acetate deprotection of **11**, we were then in a position to examine ring closure reactions to form the pyrrolizidine skeleton. Ozonolysis of the alkene yielded aldehyde **12**, which after exposure to mild conditions for *N*-Boc deprotection ($ZnBr_2$

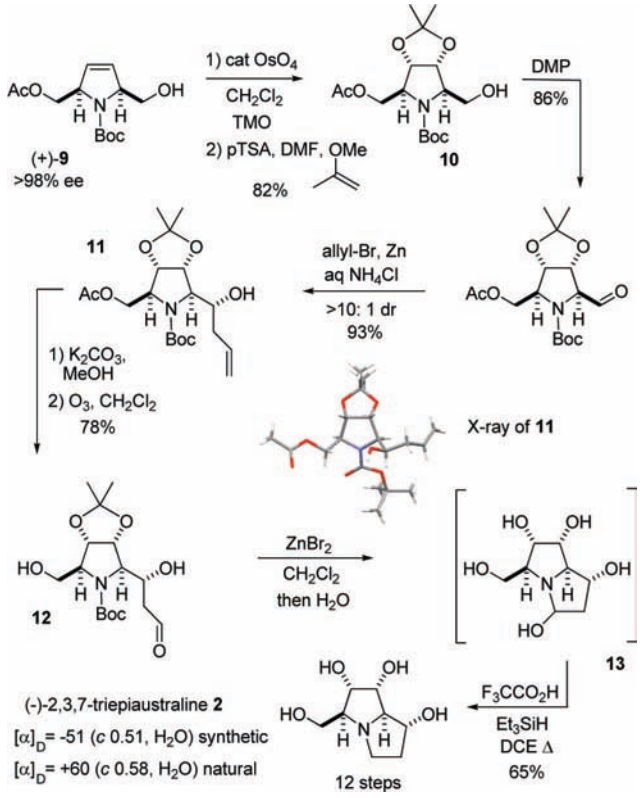
(6) (a) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A.; Sanchez-Cantlejo, F. *Tetrahedron Asymmetry* **2007**, *18*, 2211. (b) Zhou, L.; Chen, J.; Cao, X. *Synthesis* **2007**, 1359. (c) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A.; Rodriguez, M.; Martos, A. *Tetrahedron* **2006**, *62*, 6006. (d) Tang, M.; Pyne, S. G. *Tetrahedron* **2004**, *60*, 5759. (e) Tang, M.; Pyne, S. G. *J. Org. Chem.* **2003**, *68*, 7818. (f) Tayoa, A.; Tamara, O.; Takagi, H.; Ishibashi, M. *Synlett* **2003**, 35. (g) Denmark, S. E.; Cottell, J. J. *J. Org. Chem.* **2001**, *66*, 4276. (h) Ikota, N. *Tetrahedron Lett.* **1992**, *33*, 2553. (i) 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.

(7) (a) Donohoe, T. J.; Rigby, C. L.; Thomas, R. E.; Nieuwenhuys, W. F.; Bhatti, F. L.; Cowley, A. R.; Bhalay, G.; Linney, I. D. *J. Org. Chem.* **2006**, *71*, 6298. (b) Donohoe, T. J.; Headley, C. E.; Cousins, R. P. C.; Cowley, A. *Org. Lett.* **2003**, *5*, 999.

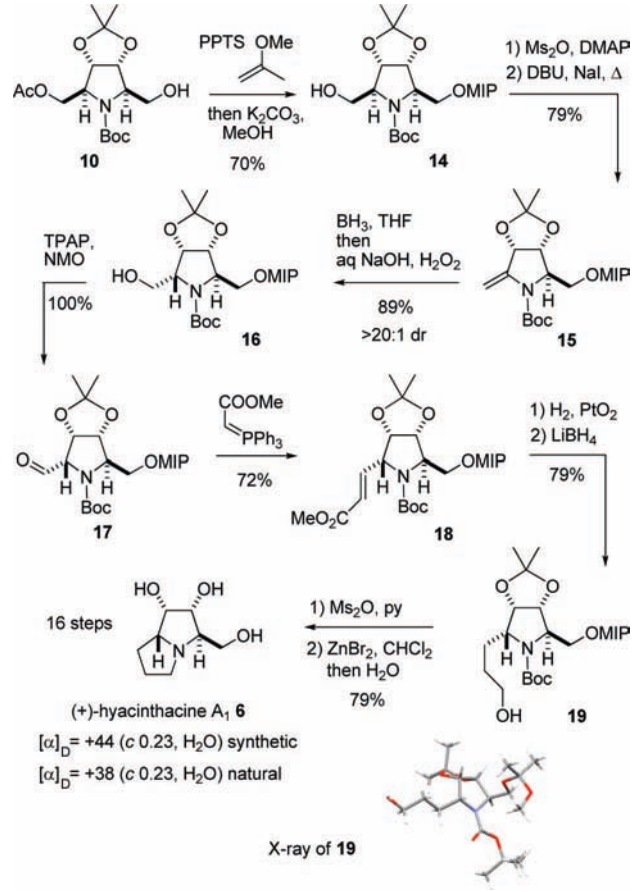
(8) Diastereoisomeric ratio was determined by examination of the crude high temperature ^{1}H NMR spectrum: Poli, G *Tetrahedron Lett.* **1989**, *30*, 7385.

(9) (a) Petrier, C.; Luche, J. L *J. Org. Chem.* **1985**, *50*, 910 For an example where these conditions gave the the Felkin-Ahn diastereomer with high selectivity, see: (b) Nagaiah, K.; Sreenu, D.; Rao, S.; Yadav, J. S. *Tetrahedron Lett.* **2007**, *48*, 7173.

Scheme 1. Synthesis of (−)-2,3,7-Triepiaustraline **2**



Scheme 2. Synthesis of (+)-Hyacinthacine A_1 **6**



in CH_2Cl_2)[10] cyclized to the bicyclic hemiaminol **13**. Finally, the aminol was reduced by the action of triethylsilane and TFA. This sequence furnished (−)-2,3,7-triepiaustraline **2** in 12 linear steps from *N*-Boc pyrrole; the spectroscopic data exhibited by this compound was almost identical to that reported for the natural product. However, the specific rotation that was measured indicated that the enantiomer as drawn is the antipode of the naturally ocurring material, and this study now confirms both the relative and absolute stereochemistry of the natural product.[3b,11]

Having established that this sequence could prepare the 2,5-*cis* (C3,7a-*cis* with natural product numbering) series of natural products very efficiently, we turned our attention toward inversion of the C-2 center as the range of 2,5-*trans* substituted natural products is much larger. Hyacinthacine A_1 **6**[3e] was chosen as an initial target on which to test this idea. Our tactics were to rely upon the large isopropylidine protecting group (at C3,4) to provide facial bias to the reaction of an enamine at C-2. Therefore, protecting group manipulation of acetate **10** gave primary alcohol **14** (MIP = $C(OMe)Me_2$), which was activated and then subjected to E2 elimination with DBU, thus furnishing enamine **15**, Scheme 2. The transformation of **14** to **15** can be performed in one pot if necessary, but the yield is lower at 49%. Stereo- and regioselective hydroboration occurred from the least hindered face, as predicted, to give the inverted alcohol at C-2 as a single diastereoisomer;[12] this alcohol **16** was then oxidized to the aldehyde **17** in good overall yield.

Slightly different tactics were employed to form the second ring, with the aim of synthesizing hyacinthacine A_1 **6**. Wittig olefination of **17** gave **18** and then exhaustive reduction of the unsaturated ester furnished primary alcohol **19**, Scheme 2.

Subsequent mesylation of alcohol **19** (Ms_2O) was followed by mild *N*-Boc deprotection (and spontaneous *in situ* cyclization) using $ZnBr_2$ in dichloromethane. Finally, the $ZnBr_2$ reaction was acidified by the addition of water to allow deprotection of the acetal, and this protocol furnished (+)-hyacinthacine A_1 **6** in 16 steps.[3e,13] The spectroscopic data was again a good match with that reported in the literature; the specific rotation was also in accordance with that given for the natural product.

With the Wittig chain extension and S_N2 ring closure chemistry working well, we decided to carry out the synthesis

(10) Nigam, S. C.; Mann, A.; Taddei, M.; Wermuth, C. G. *Synth. Commun.* **1989**, *19*, 3139.

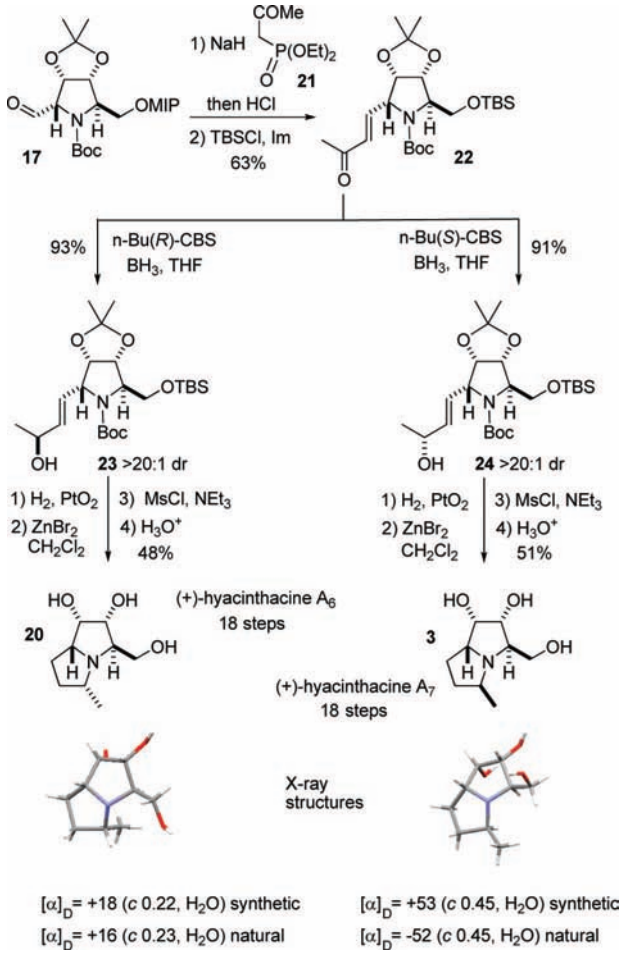
(11) (+)-2,3,7-Triepiaustraline was synthesised prior to its isolation as a natural product: Ikota, N.; Nakagawa, H.; Ohno, S.; Noguchi, K.; Okuyama, K *Tetrahedron* **1998**, *54*, 8985.

(12) Tenaka, K.-I.; Maesoba, T.; Sawanishi, H. *Heterocycles* **2006**, *68*, 183.

(13) Hyacinthacine A_1 has previously been synthesized as the racemate by: (a) Donohoe, T. J.; Sintim, H. O.; Hollinshead, J. *J. Org. Chem.* **2005**, *70*, 7297. It was synthesized asymmetrically by: (b) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2005**, *7*, 2587. (c) Izquierdo, I.; Plaza; Tamayo, J. A.; Sanchez-Cantalejo, F. *Eur. J. Org. Chem.* **2007**, 6078.

of methyl substituted hyacinthacines A_6 **20** and A_7 **3**[3c] by examining a stereospecific S_N2 displacement at a secondary center, Scheme 3.

Scheme 3. Synthesis of (+)-Hyacinthacine A_6 and A_7



The route was modified by a change of Witting reagent to keto-phosphonate **21** to furnish ketone **22** from aldehyde **17** directly (after a protecting group exchange from OMIP to OTBS that simplified matters later on).[14] Subsequent reduction of the vinyl-methyl ketone with either enantiomer of the CBS reducing agent gave diastereoisomers **23** and **24** respectively with greater than 20:1 diastereoselectivity in each case.[15] The end-game was similar to that worked out for hyacinthacine A_1 **6**, comprising alkene reduction (H_2, PtO_2), *N*-Boc deprotection ($ZnBr_2$, CH_2Cl_2), secondary alcohol activation (MsCl, with *in situ* ring closure), and finally global deprotection with aqueous acid.

The stereochemistry of the two final natural products **20** and **3** was initially assigned by determining the sense of stereoselectivity predicted for the CBS reagent with vinyl-methyl ketones, followed by an inversion reaction during ring closure.[16] As is often the case with this class of compounds, the NMR data of the natural products was a good, but not perfect, match with that reported in the literature. However, the match was close enough for us to confidently assign the structures as being those of the two natural products.[3c,17] Finally, proof of the structure of the products that we had made was obtained with single crystal X-ray analysis of both synthetic samples of the natural products (see Supporting Information). The specific rotation value of hyacinthacine A_6 **20**[18] was in accord with the literature, whereas that of A_7 **3** showed that the natural product has the opposite absolute stereochemistry to the structure as drawn.

To conclude, we have outlined a new route to the synthesis of enantiopure pyrrolizidine alkaloids starting from the key intermediate (+)-**9**. Elaboration of this compound can be accomplished in many different ways, which gives great flexibility with regards to the number and nature of the targets that can be accessed. We have proven the versatility and efficiency of this chemistry with syntheses of four different natural products and assigned the absolute configuration of two of them.

Acknowledgment. We thank the James Black Foundation, Novartis and the EPSRC for funding this work, and Merck for unrestricted support. We also thank the Oxford Chemical Crystallography Service for use of the instrumentation.

Supporting Information Available: Detailed spectroscopic data for new compounds and representative experimental procedures, plus X-ray data for compounds **11**, **19**, **20**, and **3**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL801415D

(14) The O-MIP protecting group proved too unstable to complete the synthesis.

(15) Diastereoisomeric ratio was determined by examination of the crude high temperature ^{1}H NMR spectrum.

(16) Corey, E. J.; Helal, C. J. *Angew. Chem., Int. Ed.* **1998**, *37*, 1986.

(17) It has previously been observed that the synthetic samples of polyhydroxylated pyrrolizidines do not always match exactly the isolated NMR spectra depending on the method of purification, see: ref 13a. Wormald, M. R.; Nash, R. J.; Hrnciar, P.; White, J. D.; Molyneux, R. J.; Fleet, G. W. J. *Tetrahedron: Asymmetry* **1998**, *9*, 2549.

(18) Hyacinthacine A_6 has been previously synthesised in an asymmetric manner, see ref 13c.