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Asymmetric Synthesis of Polyhydroxylated Pyrrolizidines via Transannular Iodoamination with Concomitant *N*-Debenzylation

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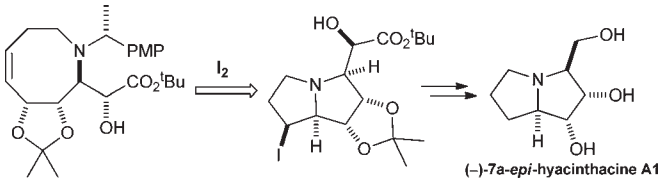
ABSTRACT



The doubly diastereoselective "matched" conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to *tert*-butyl (4*S*,5*R*,*E*)-4,5-*O*-isopropylidene-2,7-dienoate (derived from D-ribose in 3 steps) and in situ enolate oxidation with (−)-camphorsulfonyloxaziridine was followed by ring-closing metathesis with Grubbs I to give a hexahydroazocine scaffold. Subsequent treatment with I_2 resulted in transannular iodoamination accompanied by loss of the α-methyl-*p*-methoxybenzyl group to give the corresponding pyrrolizidine scaffold as a single diastereoisomer upon direct crystallization from the crude reaction mixture. Further functional group manipulations enabled the preparation of (−)-7a-*epi*-hyacinthacine A1.

Polyhydroxylated alkaloids are a subclass of alkaloids characterized by an azacyclic core with dense oxygen functionality.[1] The five main classes of polyhydroxylated alkaloids are pyrrolidines, piperidines, pyrrolizidines, indolizidines, and nortropanes.[1] Of the pyrrolizidine class, the structures of (+)-hyacinthacine A1 **1**, (+)-australine **2**, and (+)-casuarine **3** are representative of the common substitution patterns[2] (Figure 1). The biological activity of polyhydroxylated alkaloids is wide and varied, although most effects are attributed to their ability to act as glycosidase inhibitors.[3] In view of these desirable properties, a considerable amount of effort has been put into their isolation, structure elucidation, and synthesis.[2,4]

We have previously reported a novel iodine mediated ring-closing iodoamination reaction with concomitant *N*-debenzylation of an ω-unsaturated amine to generate pyrrolidine[5] and piperidine[6] scaffolds. For instance, treatment of ε,ζ-unsaturated amine **4** with I_2 and $NaHCO_3$ in MeCN gave an 81:19 mixture of diastereoisomeric iodomethyl pyrrolidines

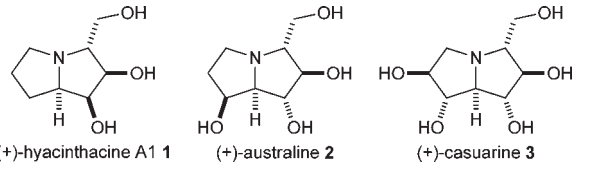


Figure 1. Structures of (+)-hyacinthacine A1 **1**, (+)-australine **2**, and (+)-casuarine **3**.

(1) Watson, A. A.; Fleet, G. W. J.; Asano, N.; Molyneux, R. J.; Nash, R. J. *Phytochemistry* **2001**, *56*, 265.
(2) Liddell, J. R. *Nat. Prod. Rep.* **2000**, *17*, 455.
(3) Winchester, B; Fleet, G. W. J. *Glycobiology* **1991**, *2*, 199. Winchester, B. *Biochem. Soc. Trans.* **1992**, *20*, 699. Winchester, B. *Tetrahedron: Asymmetry* **2009**, *20*, 645.
(4) Davis, B. G. *Tetrahedron: Asymmetry* **2009**, *20*, 652.

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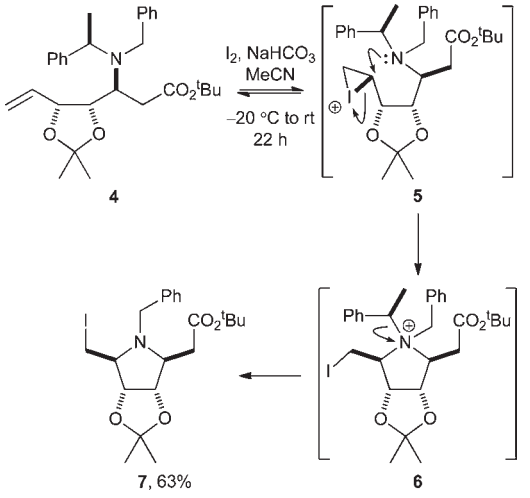
from which the major diastereoisomer **7** was isolated in 63% yield.[5] The mechanism of this transformation was proposed to involve reversible iodonium ion formation from **4** followed by preferential cyclization of iodonium **5** to give ammonium **6**. Preferential S_N1-type loss of the α-methylbenzyl group[7] from the sterically congested nitrogen atom within ammonium **6** then gave pyrrolidine **7** (Scheme 1).[5]

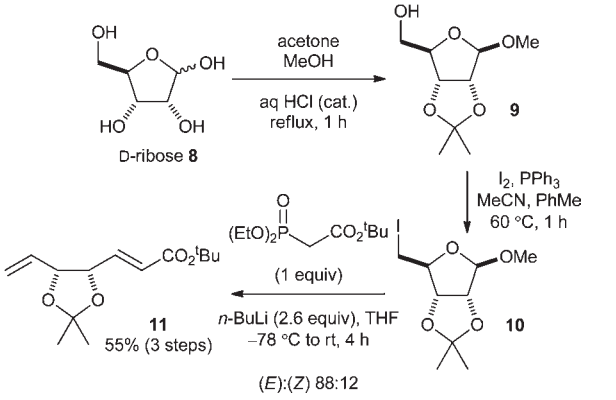
Scheme 1



Herein we report an application of this methodology to the synthesis of polysubstituted pyrrolizidines using transannular iodoamination of a hexahydroazocine scaffold[8] with concomitant *N*-debenzylation. This enables the rapid and efficient assembly of this densely functionalized molecular architecture, as demonstrated by a short asymmetric synthesis of (−)-7a-*epi*-hyacinthacine A1.[9]

An improved synthesis of *tert*-butyl (4*S*,5*R*,*E*)-4,5-*O*-isopropylidene-2,7-dienoate **11** from D-ribose **8** was developed.[10] Treatment of D-ribose **8** with acetone and methanol in the presence of HCl gave **9**, which underwent reaction with I_2 and PPh_3 to give iodide **10**.[11] Treatment of a 1:1 mixture of iodide **10** and *tert*-butyl diethylphosphonoacetate in THF with *n*-BuLi[12] promoted a tandem transmetalation/ring-opening/Wadsworth−Emmons olefination sequence of reactions to give an 88:12 (*E*)/(*Z*) mixture of olefin isomers, with chromatographic separation giving the desired (*E*)-isomer **11** as a single diastereoisomer in 55% yield from D-ribose **8** (Scheme 2).

Scheme 2



The doubly diastereoselective "matched"[13] conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide **12**[14] (99% ee)[15] to α,β-unsaturated ester **11**[16] followed by in situ enolate oxidation with (−)-camphorsulfonyloxaziridine [(−)-CSO] **13** and chromatographic purification gave α-hydroxy-β-amino ester **14** as a single diastereoisomer in 56% isolated yield.[17] The absolute configuration within **14** was assigned by analogy to the well established stereochemical outcome of our aminohydroxylation process.[5b,18] Ring-closing metathesis upon treatment of **14** with Grubbs I,[14,19] and using $P(CH_2OH)_3$ to remove the spent catalyst,[14,20] gave hexahydroazocine **15** in 86% isolated yield. Transannular iodoamination of **15** was attempted under a range of conditions, with treatment with I_2 (3 equiv) and $NaHCO_3$ (3 equiv) in $CHCl_3$ giving ammonium **16** as a single diastereoisomer, which was isolated in 70% yield after direct crystallization from the crude reaction mixture. The relative configuration

(5) (a) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Smith, A. D. *Synlett* **2004**, 901. (b) Davies, S. G.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Savory, E. D.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2009**, *20*, 758.

(6) Davies, S. G.; Hughes, D. G.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Smith, A. D.; Thomson, J. E.; Williams, O. M. H. *Synlett* **2010**, 567.

(7) The α-methylbenzyl cation is then trapped by MeCN, with the ensuing Ritter reaction giving racemic α-methylbenzyl acetamide.

(8) For an approach to polyhydroxylated pyrrolizidines employing epoxidation of a hexahydroazocine scaffold and subsequent transannular cyclization, see: White, J. D.; Hrnciar, P. *J. Org. Chem.* **2000**, *65*, 9129. Lauritsen, A.; Madsen, R. *Org. Biomol. Chem.* **2006**, *4*, 2898.

(9) For a previous synthesis of (±)-7a-*epi*-hyacinthacine A1, see: (a) Affolter, O.; Baro, A.; Frey, W.; Laschat, S. *Tetrahedron* **2009**, *65*, 6626. For a previous synthesis of (+)-7a-*epi*-hyacinthacine A1, see: (b) Izquierdo, I.; Plaza, M. T.; Tamayo, J. A.; Franco, F.; Sánchez-Cantalejo, F. *Tetrahedron* **2010**, *66*, 3788. For a previous synthesis of (−)-7a-*epi*-hyacinthacine A1, see: (c) Garrabou, X.; Gomez, L.; Joglar, J.; Gil, S.; Parella, T.; Bujons, J.; Clapes, P. *Chem.—Eur. J.* **2010**, *16*, 10691.

(10) Davies, S. G.; Durbin, M. J.; Goddard, E. C.; Kelly, P. M.; Kurosawa, W.; Lee, J. A.; Nicholson, R. L.; Price, P. D.; Roberts, P. M.; Russell, A. J.; Scott, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2009**, *7*, 761.

(11) Paquette, L. A.; Bailey, S. *J. Org. Chem.* **1995**, *60*, 7849.

(12) Modification of the procedure reported by Palmer, A. M.; Volker, J. *Eur. J. Org. Chem.* **2001**, 1293.

(13) Masamune, S.; Choy, W.; Petersen, J. S.; Sita, L. R. *Angew. Chem., Int. Ed. Engl.* **1985**, *24*, 1.

(14) Davies, S. G.; Fletcher, A. M.; Roberts, P. M.; Smith, A. D. *Tetrahedron* **2009**, *65*, 10192.

(15) Enantiopure (*R*)-α-methylbenzylamine (99% ee) is commercially available. Alkylation of (*R*)-α-methylbenzylamine upon treatment with 4-bromobut-1-ene in the presence of K_2CO_3 gave (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amine; subsequent deprotonation with *n*-BuLi in THF generated a yellow solution of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methylbenzyl)amide **12**.

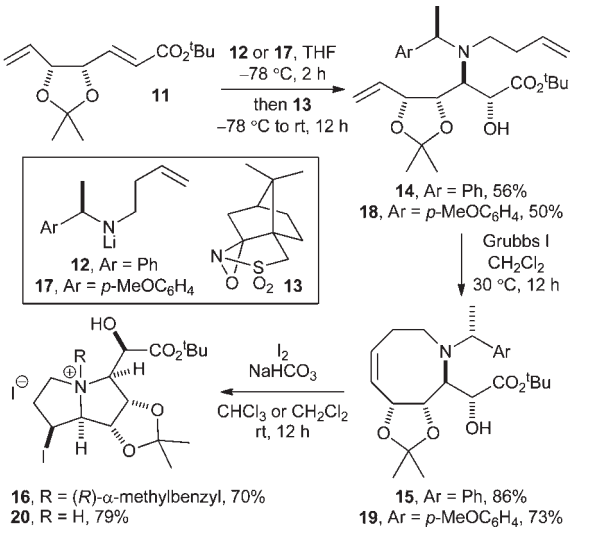
(16) For determination of the "matched" and "mismatched" reaction pairings for the additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to chiral α,β-unsaturated ester **11**, see ref 10.

(17) Both the α-hydroxy-β-amino ester (**14** or **18**) and the corresponding β-amino ester (**14P** or **18P**) were present in the crude reaction mixture.

within **16** was unambiguously assigned by single crystal X-ray analysis,[21] with the absolute configuration following from the known (*R*)-configuration of the *N*-α-methylbenzyl stereocenter and the C(1)- and C(2)-stereocenters derived from D-ribose. This analysis also affirms the absolute configurations assigned to *β*-amino ester **14** and hexahydroazocine **15**.

The observation that ammonium **16** is the major product from transannular iodoamination of hexahydroazocine **15** is in contrast to our observations concerning the cyclization of *ε*,*ζ*-unsaturated amine **4** in which *N*-debenzylation of ammonium **6** occurs readily in situ by an S_N1 pathway.[5] Unfortunately, attempted removal of the α-methylbenzyl group from **16** under a range of conditions failed, and therefore the incorporation of an α-methyl-*p*-methoxybenzyl group (in place of an α-methylbenzyl group) into the hexahydroazocine scaffold was investigated in an effort to promote an S_N1-type reaction pathway. Thus, aminohydroxylation of **11** using the doubly diastereoselective "matched"[13] conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **17**[16] (>99% ee)[22] and in situ enolate oxidation with (−)-CSO **13** gave α-hydroxy-*β*-amino ester **18** as a single diastereoisomer in 50% isolated yield.[17] Ring-closing metathesis of **18**[14,19] gave hexahydroazocine **19** in 73% isolated yield. Under optimized conditions, transannular iodoamination of **19** in CH_2Cl_2 (EtOH stabilized) was accompanied by concomitant loss of the α-methyl-*p*-methoxybenzyl group (presumably via an S_N1-type process to generate the corresponding cation) resulting in production of the corresponding pyrrolizidine that was isolated as the hydroiodide salt **20** in 79% yield upon direct crystallization from the crude reaction mixture. Concentration of the mother liquors and chromatographic purification of the residue gave α-methyl-*p*-methoxybenzyl ethyl ether **21** in 95% yield, consistent

Scheme 3



with trapping of the α-methyl-*p*-methoxybenzyl cation by the EtOH stabilizer present in the reaction solvent[23] (Scheme 3). The relative configuration within **20** was unambiguously established by single crystal X-ray analysis,[24] with the absolute configuration being assigned from the known configurations of the C(1)- and C(2)-stereocenters derived from D-ribose **8**. This analysis also secures the assigned absolute configurations within *β*-amino ester **18** and hexahydroazocine **19**.

The homochirality of **16** and **20** suggests an identical mechanism of cyclization. The observed stereochemical outcome of this process is presumably controlled by reversible iodonium formation from hexahydroazocine scaffolds **15** and **19** followed by preferential transannular reaction of one of the corresponding diastereoisomeric iodonium ions. Transannular reaction of iodoniums **22** (Ar = Ph) or **23** (Ar = PMP) is expected to be disfavored due to the high degree of 1,2-strain between the *N*-protecting group (R*) and the adjacent substituent (R); transannular reaction of iodoniums **24** (Ar = Ph) or **25** (Ar = PMP) does not suffer from such a severe steric interaction and results in the production of the corresponding ammoniums **16** (Ar = Ph) and **26** (Ar = PMP). Subsequent S_N1-type loss of the *N*-protecting group under the reaction conditions occurs only in the case of *N*-α-methyl-*p*-methoxybenzyl protected **26**, leading to the formation of pyrrolizidine **27** which undergoes salt formation with in situ generated HI to give **20** (Figure 2).

The utility of this approach to enable the synthesis of polyhydroxylated pyrrolizidine natural products and their diastereoisomers was next demonstrated by application to a short asymmetric synthesis of (−)-7a-*epi*-hyacinthacine A1 **30**.[9] Reduction of pyrrolizidine hydroiodide salt **20** with $LiAlH_4$ gave diol **28** in 87% isolated yield after chromatography. Oxidative cleavage of diol **28** was effected upon treatment with $NaIO_4$ in $MeOH/H_2O$ and was followed immediately by treatment of the reaction mixture with

(18) For selected examples, see: Bunnage, M. E.; Burke, A. J.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2003**, *1*, 3708. Abraham, E.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Smith, A. D.; Thomson, J. E. *Tetrahedron: Asymmetry* **2007**, *18*, 2510. Abraham, E.; Davies, S. G.; Millican, N. L.; Nicholson, R. L.; Roberts, P. M.; Smith, A. D. *Org. Biomol. Chem.* **2008**, *6*, 1655. Abraham, E.; Brock, E. A.; Candela-Lena, J. I.; Davies, S. G.; Georgiou, M.; Nicholson, R. L.; Perkins, J. H.; Roberts, P. M.; Russell, A. J.; Sánchez-Fernández, E. M.; Scott, P. M.; Smith, A. D.; Thomson, J. E. *Org. Biomol. Chem.* **2008**, *6*, 1665.

(19) Davies, S. G.; Iwamoto, K.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Synlett* **2002**, 1146. Chippindale, A. M.; Davies, S. G.; Iwamoto, K.; Parkin, R. M.; Smethurst, C. A. P.; Smith, A. D.; Rodriguez-Solla, H. *Tetrahedron* **2003**, *59*, 3253.

(20) Maynard, H. D.; Grubbs, R. H. *Tetrahedron Lett.* **1999**, *40*, 4137.

(21) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 805283.

(22) Enantiopure (*R*)-α-methyl-*p*-methoxybenzylamine (>99% ee) is commercially available. Alkylation of (*R*)-α-methyl-*p*-methoxybenzylamine upon treatment with 4-bromobut-1-ene in the presence of K_2CO_3 gave (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amine; subsequent deprotonation with *n*-BuLi in THF generated a yellow solution of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)-amide **17**.

(23) See also: Srihari, P.; Bhunia, D. C.; Sreedhar, P; Yadav, J. S. *Synlett* **2008**, *7*, 1045.

(24) Crystallographic data (excluding structure factors) have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 805284.

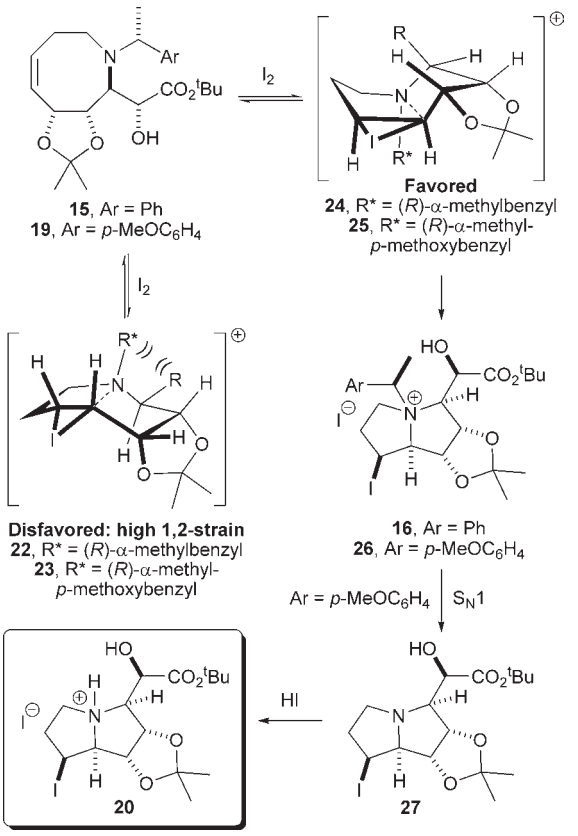
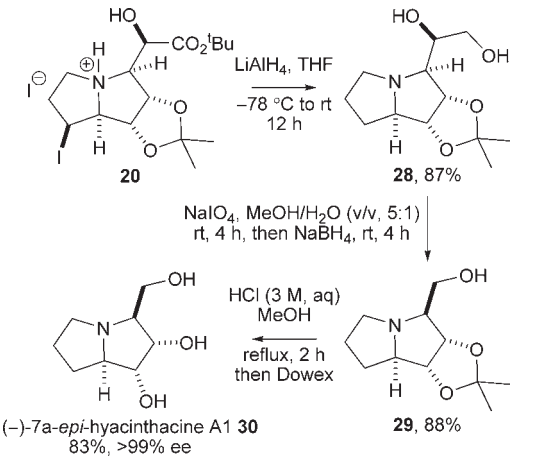


Figure 2. Postulated mechanistic rationale for transannular iodoamination of hexahydroazocines **15** and **19**. R = (*R*)-CH(OH)$CO_2{}^t$Bu.

$NaBH_4$ to give alcohol **29** in 88% yield over the 2 steps. Finally, hydrolysis of **29** upon treatment with 3 M aq. HCl in MeOH and purification on Dowex 1X8 200-400 (OH^- form) ion-exchange resin gave (−)-7a-*epi*-hyacinthacine A1 **30**[9] {$[\alpha]_D{}^{25}$ −45.9 (*c* 0.2 in H_2O); lit.[9c] $[\alpha]_D{}^{22}$ −45.3 (*c* 1.5 in H_2O)} in 83% isolated yield as a single diastereoisomer. Given the known enantiomeric purity of the lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide **12** (i.e., >99% ee) employed for the conjugate addition to α,β-unsaturated ester **11** (itself derived from D-ribose), the enantiomeric purity of (−)-7a-*epi*-hyacinthacine A1 **30** and intermediates **18**−**20**, **28**, and **29** can be confidently inferred as >99% ee (Scheme 4).

Scheme 4



In conclusion, the doubly diastereoselective "matched" conjugate addition of lithium (*R*)-*N*-but-3-enyl-*N*-(α-methyl-*p*-methoxybenzyl)amide to *tert*-butyl (4*S*,5*R*,*E*)-4,5-*O*-isopropylidene-2,7-dienoate (derived from D-ribose in 3 steps) and in situ enolate oxidation with (−)-camphorsulfonyloxaziridine was followed by ring-closing metathesis with Grubbs I to give a hexahydroazocine scaffold. Subsequent treatment with I_2 resulted in transannular iodoamination accompanied by loss of the α-methyl-*p*-methoxybenzyl group to give the corresponding pyrrolizidine scaffold as a single diastereoisomer upon direct crystallization from the crude reaction mixture. Further functional group manipulations enabled the preparation of (−)-7a-*epi*-hyacinthacine A1. Further applications of this transannular iodoamination protocol to facilitate the preparation of other natural and unnatural polyhydroxylated bicyclic scaffolds are currently under investigation in our laboratory.

Supporting Information Available. Experimental procedures, characterization data, copies of ^1H and ^{13}C NMR spectra, and crystallographic information files (for structures CCDC 805283 and 805284). This material is available free of charge via the Internet at http://pubs.acs.org.