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Asymmetric route to the hydroindolone core of the *Amaryllidaceae* alkaloids employing chiral bicyclic lactams

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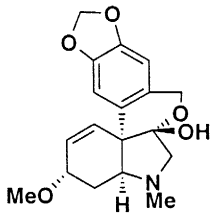
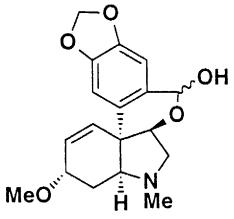
Abstract

The asymmetric synthesis of the hydroindolone core (**5**) of the *Amaryllidaceae* alkaloids employing chiral bicyclic lactams is described. The vicinal quaternary and tertiary stereocenters were assembled via an addition of lactam **14** enolate to acrolein.

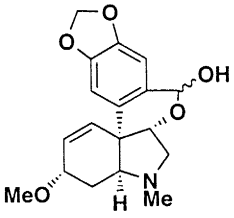
The alkaloids of the *Amaryllidaceae* family are composed of over 100 architecturally interesting natural bases and may be classified into several principal skeletally homogeneous subgroups.[1] In particular the 2-benzopyrano-(3,4-*c*)-hydroindole derived members, exemplified by tazettine (**1**), pretazettine (**2**) and 6a-epipretazettine (**3**) have captured the interest among a number of synthetic groups as targets for total synthesis due to their biological properties.



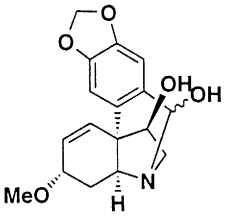
Tazettine 1



(+)-Pretazettine 2



6a-epiPretazettine 3



(-)-Haemanthidine 4

Tazettine (**1**) exhibits mild activity against certain tumor cell lines.[2] However there is more interest in the chemically labile pretazettine (**2**) owing to its antiviral and anticancer activity particularly in Rauscher leukemia, Lewis lung carcinoma and spontaneous AKR lymphocytic leukemia.[3] Pretazettine (**2**) has also been found to inhibit protein synthesis in eukaryotic cells by a mechanism which does not affect DNA and RNA synthesis.[3a] Racemic total syntheses of the 2-benzopyrano-(3,4-*c*)-hydroindole subunit of the *Amaryllidaceae* alkaloids have been reported by groups of Hendrickson,[4] Tsuda,[5] Danishefsky,[6] White,[7] Martin,[8] Overman[9] and Rigby.[10] Formal synthesis and partial synthesis of pretazettine and

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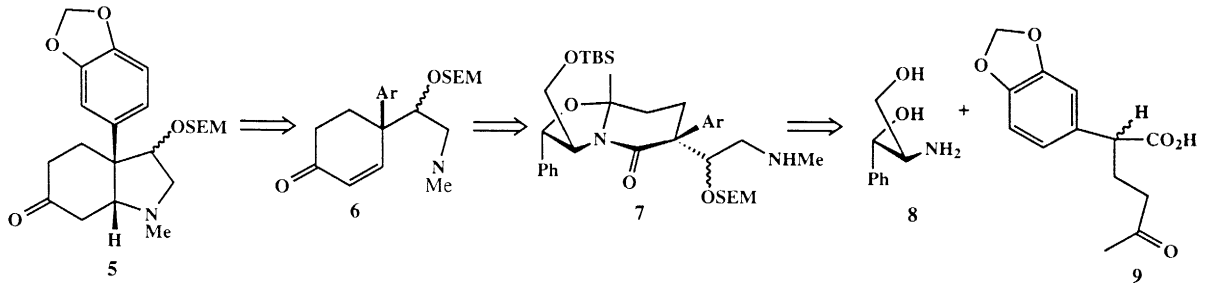
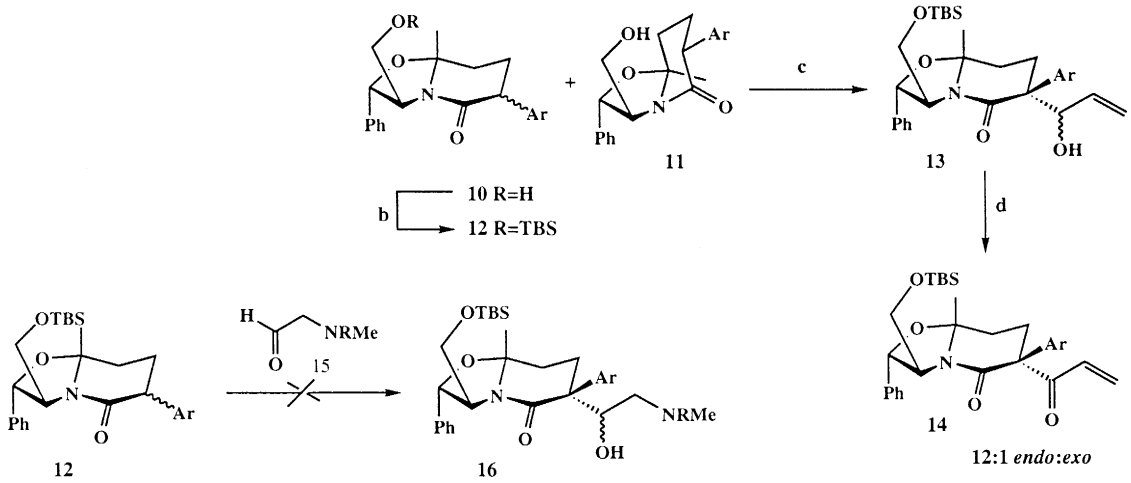
related compounds have also been reported.[11] More recently the first asymmetric total synthesis of (−)-haemanthidine (**4**) and (+)-pretazettine (**2**) has been reported by Mori et al.[12]

Our retrosynthetic analysis was based on our earlier report describing the first asymmetric synthesis of mesembrine.[13] The desired core **5** was envisioned to arise from lactam **7** and the amine appendage on the intermediate bicyclic lactam which in turn may be derived from aminoalcohol **8** and keto acid **9** (Scheme 1).



Scheme 1.

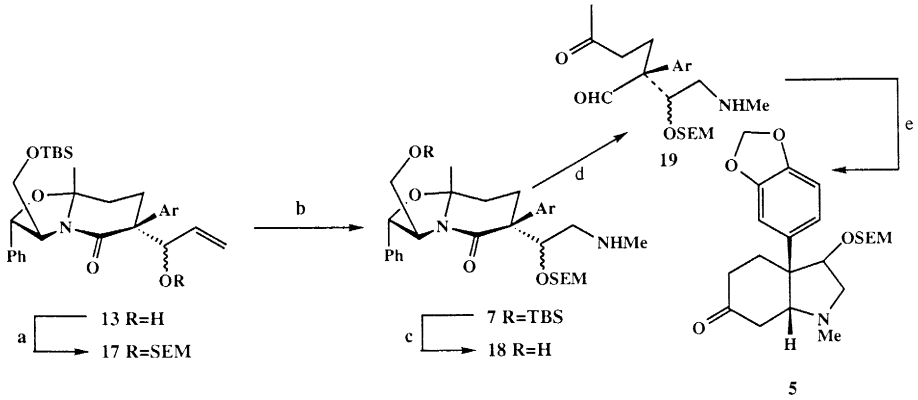
Synthesis of the requisite keto acid **9** was accomplished by basic hydrolysis (25% NaOH, MeOH) of commercially available phenylacetonitrile to provide the corresponding phenylacetic acid in quantitative yield. Following metalation (2.1 equiv. *n*-BuLi, THF) and treatment with 2-methyl-2-(2-iodoethyl)-1,3-dioxolane[14] cleavage of the ketal functionality (PPTS, EtOH, 60°C) furnished **9** in 74% overall yield after recrystallization from hexanes/ether. Condensation of **9** with (1*S*,2*S*)-(+)-2-amino-1-phenyl-1,3-propanediol (**8**) (toluene, reflux, 16 h, 73%) provided bicyclic lactams **10**, **11**, as a three component mixture of diastereomers with aryl substituents epimeric at both the α-C and angular methyl group (*endo* aryl **10**:*exo* aryl **10** and **11**, 57:23:20). Thus, 80% of the mixture (*exo–endo* **10**) is useful for the synthesis (Scheme 2).



Scheme 2. Reagents and conditions: (a) toluene, reflux, 16 h, 73%; (b) TBSCl, imid., DMAP, CH_2Cl_2, **12**, 74%, **13**, 21%; (c) LDA, (2.0 equiv.), THF, −78°C, 20 min, acrolein, 3 h, 80%; (d) Dess–Martin periodinane, CH_2Cl_2, 90%

Silylation of the 3-component mixture of primary alcohols **10**, **11** (TBDMSCl, imid. DMAP, CH_2Cl_2) furnished lactam **12** in 74% yield as a 2:1 mixture of α-C aryl diastereomers along with recovered alcohol **11** in 20–21% yield. Addition of the lithio-enolate of lactam **12** to amino aldehyde **15**[8a] (R=Boc, Bn) proved to be fruitless. However, addition of **12** (LDA, −78°C) to acrolein provided lactam **13** in 98%

yield as a 1:1 mixture of diastereomers epimeric at the newly formed hydroxy stereocenter. Dess–Martin oxidation[15] of the crude allylic alcohol **13** furnished enone **14** in 90% yield (Scheme 2). The ^{1}H NMR spectrum of **14** indicated a 12:1 diastereomeric mixture corresponding to *endo*:*exo* aryl-allylic ketone and therefore allylic alcohol **13** was also assumed to be a 12:1 mixture at the α-carbon. Interestingly, generation of the zinc enolate of **12** followed by addition of acrolein provided alcohol **13** as a 2:1 mixture of diastereomers at the hydroxyl center. Silylation[16] of the allylic alcohol **13** (SEMCl, ^{i}Pr$_2$NEt, CH_2Cl_2; 80%) then gave 2-(trimethylsilyl) ethoxymethyl acetal **17** (Scheme 3). Treatment of **17** with a catalytic amount of OsO_4 using *N*-methylmorpholine *N*-oxide as reoxidant, followed by sodium periodate cleavage[17] and reductive amination[18] ($MeNH_2 \cdot HCl$, $NaCNBH_3$, MeOH) of the resulting aldehyde gave amine **7** in 91% overall yield. Fluoride induced removal of the *tert*-butyldimethylsilyl ether (TBAF, THF, 3 h; 50%) furnished the primary alcohol **18**.



Scheme 3. Reagents and conditions: (a) SEMCl, ^{i}Pr$_2$NEt, CH_2Cl_2, 80%; (b) (i) OsO_4 (0.05 equiv.), NMO (2.0 equiv.), THF/H_2O (3:1), ^{t}BuOH, rt, 14 h, (ii) $NaIO_4$, THF/H_2O (3:1), 1 h, (iii) $CH_3NH_2 \cdot HCl$, $NaCNBH_3$, MeOH, 3 d, 91%; (c) TBAF, THF, 0°C, 30 min, rt, 3 h, 50%; (d) RedAl (2.4 equiv.), 24 h, (ii) $Bu_2NH_2PO_4$, EtOH, reflux, 21 h, (e) 4 M NaOH, 30 min, rt

It has previously been reported that reduction of the lactam carbonyl of 5,6-bicyclic lactams is often accompanied by reductive cleavage at the angular methyl position.[19] However, the presence of the primary alcohol moiety in the amino diol derived bicyclic lactam **18** allows intramolecular delivery of hydride providing after hydrolysis, 4,4-disubstituted cyclohexenones. Hence, reduction of **18** (RedAl, toluene, 24 h) followed by hydrolysis ($Bu_4NH_2PO_4$, H_2O, EtOH, reflux, 21 h) gave keto-aldehyde **19**. Treatment of **19** with 4 M NaOH for 30 min furnished the cyclohexenone **6** which spontaneously gave the hydroindolone **5** as a single diastereomer in 27% yield over three steps. Thus, the mixture at the OSEM center appeared to have been separated during the three step sequence and flash chromatography (Scheme 3). At this point we have not confirmed the stereochemistry of the SEM ether.

In summary, a general route to the hydroindolone core of the *Amaryllidaceae* alkaloids has been developed from chiral non-racemic bicyclic lactams which after some routine synthetic steps should be in a position to reach the four members (**1**–**4**) of the *Amarylidaceae* alkaloids. Further studies are in progress to enhance the stereoselectivity of acrolein addition to **12**, as well as completion of the synthetic routes depicted to reach these alkaloids.

Acknowledgements

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