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# A new entry to *Amaryllidaceae* alkaloids from carbohydrates: total synthesis of (+)-vittatine†

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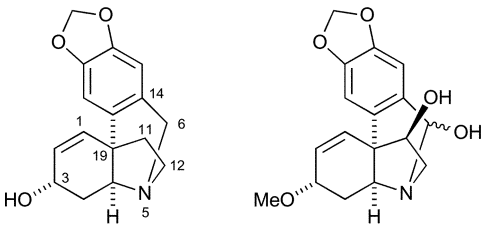
**The stereoselective and chiral synthesis of the *Amaryllidaceae* alkaloid, (+)-vittatine 1, is described; the quaternary carbon in 1 was generated by Claisen rearrangement of a cyclohexenol derived from D-glucose by way of a Ferrier's carbocyclisation reaction and a hexahydroindole skeleton was effectively constructed by intramolecular aminomercuration–demercuration, followed by Chugaev reaction.**

Ferrier's carbocyclisation reaction is one of the most useful transformations for the construction of optically pure cyclohexanone derivatives from aldohexoses.[1] Chiral and highly functionalized cyclohexanes obtained by this reaction are potentially versatile chiral building blocks in natural product synthesis.[2] Here we report a stereoselective and chiral total synthesis of (+)-vittatine **1**, an *Amaryllidaceae* alkaloid, starting from D-glucose. (+)-Vittatine[3] is the enantiomer of (−)-crinine, a representative natural product of the crinine class of alkaloids, and has a basic skeleton with the same absolute configuration as that of the more pharmacologically active crinane class of alkaloids such as haemanthidine, pretazettine and tazettine.[4] Although a number of synthetic approaches towards crinine and the crinan class of alkaloids have been developed,[5] reports on chiral syntheses of these natural products[6] are limited. Since these alkaloids are known to show a wide range of biological activities,[4] it is still important to establish a chiral and effective synthetic route to these compounds from readily available materials.

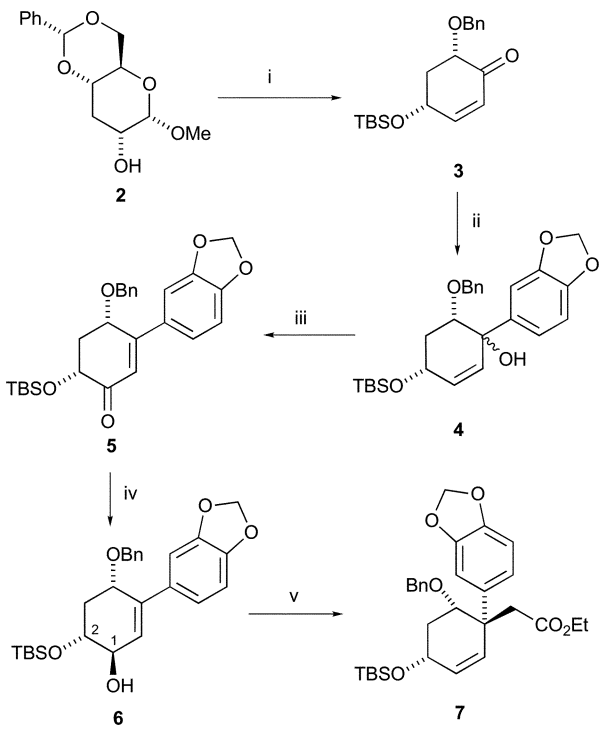



(+)-vittatine **1** (–)-haemanthidine

Synthesis of **1** commenced from 3-deoxy-D-glucose derivative[7] **2** prepared from commercially available methyl 4,6-*O*-benzylidene-α-D-glucopyranoside in two steps (75% overall yield). Compound **2** was converted into the known chiral cyclohexenone **3**[2a]‡ by the procedure developed in our laboratory using catalytic Ferrier's carbocyclisation reaction[8] as the key transformation (total 5 steps, 50% overall yield) (Scheme 1). Reaction of **3** with 3,4-(methylenedioxy)phenylmagnesium bromide at −100 °C gave 1,2-adduct **4** as a diastereomeric mixture (*ca.* 3 : 1) in 92% yield. Oxidation of **4** with PCC afforded cyclohexenone **5**, which was reduced under the conditions of Luche[9] at −78 °C to give allyl alcohol **6** and its diastereomeric alcohol in 68 and 7% yields from **4**, respectively. The observed coupling constant in **6** ($J_{1,2}$ = 7.8 Hz) supported the assigned configuration. Claisen rearrangement of **6** with triethyl orthoacetate in the presence of powdered molecular sieves 4A and a catalytic amount of propionic acid[10] at 130 °C successfully constructed the quaternary carbon to provide the rearranged product **7** in 60% yield (starting material **6** was recovered in 10% yield).

† Electronic Supplementary Information (ESI) available: experimental details. See http://www.rsc.org/suppdata/cc/b4/b402762k/

Reduction of the ester function in **7** with DIBAL-H gave primary alcohol **8** (97% yield), to which was introduced an amino function by Mitsunobu amination[11] to afford **9** in 98% yield (Scheme 2). Treatment of **9** with Na–naphthalene[12] in THF at −40 °C removed *N*-Ts as well as *O*-benzyl groups to give **10** in 77% yield. The construction of the perhydroindole skeleton was successfully achieved by intramolecular aminomercuration–demercuration[10b,13] of **10** to provide **11** in 75% yield.§ The requisite carbon–carbon double bond between C(1) and C(2) was introduced by Chugaev reaction. Thus, the hydroxy group in **11** was transformed into xanthate ester, and this was heated at 160 °C in the presence of potassium carbonate to provide **12** in 80% yield. Deprotection of the *N*-Boc group by the action of $BF_3{\cdot}OEt_2$ gave **13** (78% yield, starting material **12** was recovered in 14% yield). Exposure of **13** to the conditions of the Pictet–Spengler reaction[5b] generated the fourth ring between N(5) and C(14) and induced the deprotection of the *O*-TBS group to furnish (+)-vittatine **1** in 51% yield. The $^1$H NMR data ($CDCl_3$)¶ were fully identical with those for (−)-crinine reported by Pearson[5c] and physical properties of **1** showed good agreement {mp 205–207 °C; $[\alpha]_D^{22}$ +28 (*c* 0.20, $CHCl_3$)} with those reported for natural (+)-vittatine[3b] {mp 207–208 °C; $[\alpha]_D^{25}$ +26 (*c* 0.5, $CHCl_3$)}.




**Scheme 1** Bn = –$CH_2$Ph, TBS = –$SiMe_2$(*t*-Bu). *Reagents and conditions*: i (1) diisobutylaluminium hydride (DIBAL-H), toluene, rt, (2) $I_2$, $Ph_3P$, imidazole, toluene, (3) TBSCl, imidazole, DMF; (4) *t*-BuOK, THF; (5) $Hg(OCOCF_3)_2$ (30 mol%), acetone–acetate buffer (1 : 1), rt, then MsCl, $Et_3N$, $CH_2Cl_2$ (see ref. 2*a*); ii 3,4-(methylenedioxy)phenyl bromide, Mg, THF, −100 °C; iii PCC, MS4A, $CH_2Cl_2$, rt; iv $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH–$CH_2Cl_2$ (1 : 1), −78 °C; v $CH_3C(OEt)_3$, cat. EtCOOH, MS4A, 130 °C, 48 h, in a sealed tube.

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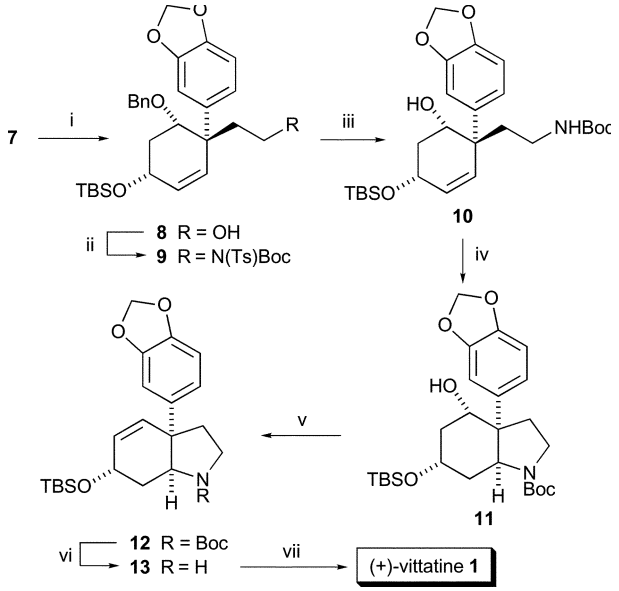


**Scheme 2** Ts = $-C_6H_4$(*p*-Me), Boc = $-C(O)OCMe_3$. *Reagents and conditions*: i DIBAL-H, toluene, −78 °C; ii NH(Ts)Boc, $PPh_3$, diethyl azodicarboxylate. THF, rt; iii Na–naphthalene, THF, −40 °C, 90 min; iv $Hg(OCOCF_3)_2$, THF, rt, then $NaBH_4$, 0.5 M aq. NaOH–MeOH, rt; v NaH, $CS_2$, MeI, THF, then 1,2-dichlorobenzene, $K_2CO_3$, MS4A, 160 °C; vi $BF_3{\cdot}OEt_2$, MS4A, $CH_2Cl_2$, rt; vii formalin, 6 M aq. HCl–MeOH, 50 °C.

In summary, transformation of a readily available carbohydrate, D-glucose, into the representative *Amaryllidaceae* alkaloid, (+)-vittatine **1**, has been achieved. This is the first asymmetric synthesis of **1** and further study on synthesis of structurally more complex alkaloids in this class such as haemanthidine and tazettine based on the same strategy is under investigation in our laboratory.

## Notes and references

‡ Cyclohexenone **3** was used as the key intermediate for our total synthesis of (−)-actinobolin. See ref. 2(*a*).

§ Similar aminomercuration gave no cyclised product when the corresponding amine (with no Boc group) was employed as the substrate.

¶ In the $^1H$ and $^{13}C$ NMR of vittatine in $CDCl_3$ (treated with alumina prior to measuring to remove residual DCl), chemical shifts of some signals were found to vary significantly by the concentration of the sample. Such concentration dependence was not observed when spectra were measured in pyridine-$d_5$.


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