Total Synthesis of (+)-Hyacinthacine A_6 and (+)-Hyacinthacine A_7

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Abstract: (+)-Hyacinthacines A_6 and A_7 have been synthesized from a common, late-stage intermediate, prepared in high yield through stereoselective [2+2] cycloaddition of dichloroketene to a chiral enol ether. The flexibility of aminonitrile chemistry is central to the approach.

Key words: asymmetric synthesis, cycloaddition, glycosidase inhibitors, aminonitriles, iminosugars

Iminosugars are carbohydrate analogues in which the ring oxygen has been replaced with nitrogen.[1] Their resemblance to carbohydrates and the presence of the endocyclic nitrogen make them powerful glycosidase inhibitors.[2] Theses enzymes, which catalyze the hydrolysis of oligosaccharides and glycoconjugates, are involved in a large array of biological processes (cell–cell and cell–virus interactions, for example).[3] Inhibitors of these enzymes are thus potential drugs against various human pathologies.[4]

Among the different naturally occurring iminosugars, the hyacinthacine alkaloids have received particular attention over the past few years due to their selective inhibition profile.[5] These polyhydroxylated pyrrolizidines are characterized by the presence of an hydroxymethyl substituent at C-3 and are designated A, B, or C on the basis of the number of hydroxyl and hydroxymethyl substituents present on ring B of the pyrrolizidine skeleton (Figure 1).[6] Most of the synthetic effort reported to date toward the hyacinthacines has focused on the A group members hyacinthacines A_1 (**1**) and A_2.[7] The other members of the A group are synthetically more challenging C-3 and C-5 disubstituted pyrrolizidines (e.g., **2**–**4**), and they have, perhaps as a consequence, received much less attention. In this communication, a highly stereocontrolled, nonchiral pool, nonenzymatic approach to hyacinthacines A_6 and A_7 is described.[8]

The published[9,10] syntheses of hyacinthacines A_6 and A_7 have all relied on chiral-pool material or enzymatic techniques for chirality. We believed that our asymmetric dichloroketene–chiral enol ether cycloaddition methodology,[11] previously applied for the preparation of a variety of alkaloids,[12–15] coupled with flexible aminonitrile chemistry,[16] might offer attractive alternative access to these two diastereomeric C-3,C-5-disubstituted hyacinthacines. The syntheses began with the previously reported,[15c] highly stereoselective preparation of benzylidene-protected dihydroxypyrrolizidinone **7** from (*S*)-(–)-stericol **5**, an efficient and commercially available chiral auxiliary.[17] Benzylidene diol protection was chosen not only for its general ease of introduction and removal, but also because of the expected stereochemical directing effect of the *endo* phenyl group (Scheme 1).

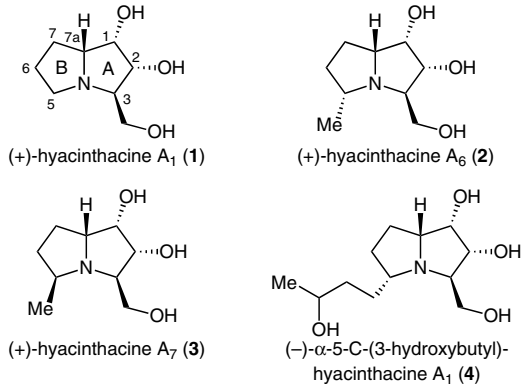
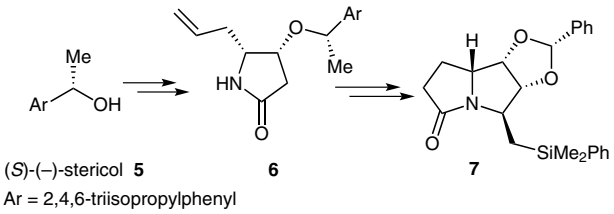


Figure 1 Examples of group A hyacinthacines



Scheme 1 Preparation of protected dihydroxypyrrolizidinone **7**[15c]

To obtain hyacinthacine A_6 from pyrrolizidinone **7**, a methyl group needed to be introduced at C-5 on the more crowded *endo* face of the tricyclic structure. It appeared that this might prove feasible through methylation–reduction of the corresponding aminonitrile.[15c] Reductive cyanation (partial hydride reduction[18] of the lactam, followed by TMSCN treatment) was thus effected to produce in high yield an inconsequential mixture of the two epimeric aminonitriles **8**. Deprotonation of this mixture with LDA, in the absence of all oxygen,[19] followed by addition of excess methyl iodide, then yielded a mixture of the corresponding methylated aminonitriles **9**. This crude material was not stable toward purification and was therefore directly reduced with sodium borohydride to generate a somewhat disappointing 3:1 mixture of the desired methyl-substituted pyrrolizidine **10** and its C-5 epimer. Fortunately, however, a much improved 10:1 ratio was produced by using Super-Hydride as the reducing agent

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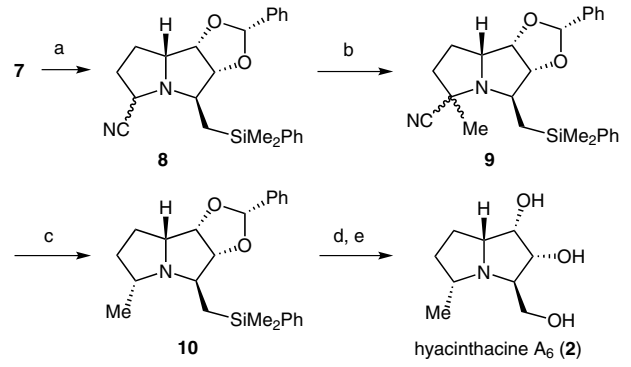
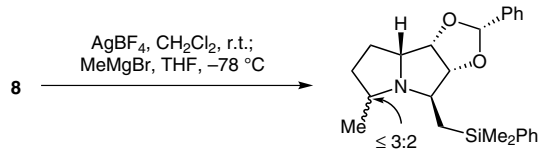
and the major isomer **10** could be isolated in 78% overall yield (Scheme 2).



Scheme 2 *Reagents and conditions*: (a) DIBAL-H, *n*-BuLi, THF, TMSCN, 97%; (b) LDA, THF, MeI; (c) $LiEt_3BH$, THF (dr = 10:1), SiO_2, 78% (2 steps); (d) KH, *t*-BuOOH, TBAF, DMF, 70%; (e) HCl, MeOH, 73%.

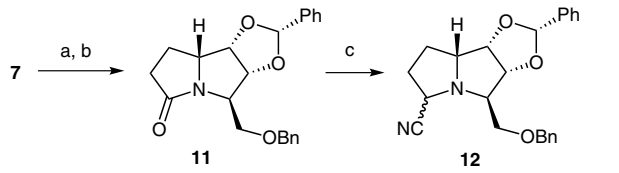
The C-3 hydroxymethyl substituent was next unmasked by Tamao–Fleming oxidation,[20] without concomitant formation of the *N*-oxide, under the basic conditions described by Smitrovich and Woerpel.[21] Acid cleavage of the acetal then completed the synthesis of hyacinthacine A_6, which was isolated in 73% yield after basic resin column chromatography. The spectroscopic data provided by the synthetic material were in accordance with those reported for natural hyacinthacine A_6 {$[\alpha]_D$ +18.0, lit.[8] $[\alpha]_D$ +16.3}.

It was hoped that hyacinthacine A_7 might be accessed from the same mixture of aminonitriles **8** by using a Bruylants reaction,[22] since in this reaction attack of an alkyl Grignard reagent would be expected to occur on the *exo* face, opposite the phenyl. Yu and coworkers,[23] however, had found that methyl Grignard lacks sufficient reactivity in this type of reaction and requires initial formation of the iminium salt for a successful application. Therefore, the aminonitriles **8** were treated first with silver tetrafluoroborate and then with methylmagnesium bromide, which indeed provided the expected methylated pyrrolizidines but, to our dismay, as a nearly equimolar mixture of isomers (≤3:2, Equation 1).



Equation 1

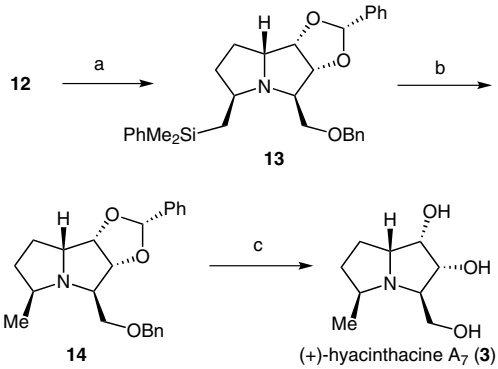
This poor facial discrimination led us to reduce the steric impediment of the C-3 *exo* substituent in **8** by performing the Tamao–Fleming oxidation before introduction of the C-5 methyl. This steric modification (a protected hydroxymethyl in place of the bulky dimethylphenylsilylmethyl) could be readily achieved by applying the Smitrovich and Woerpel conditions[21] to pyrrolizidinone **7** to give in 70% yield the C-3 hydroxymethyl derivative, which was smoothly protected as the benzyl ether **11** by using sodium hydride and benzyl bromide (83%). The new aminonitriles **12** were then prepared by reductive cyanation in 68% yield (Scheme 3).



Scheme 3 *Reagents and conditions*: (a) KH, *t*-BuOOH, TBAF, DMF, 70%; (b) NaH, DMF, BnBr, TBAI, 83%; (c) DIBAL-H, *n*-BuLi, THF, TMSCN, 68%.

In the key event, treatment of these aminonitriles **12**, first with $AgBF_4$ and then with MeMgBr, did indeed afford the corresponding methylated derivative in an improved 2:1 ratio of diastereomers, but this was nevertheless still unacceptably low (not shown).

In order to further differentiate the levels of face–reagent steric interaction, the use of a bulky methyl equivalent was next considered. In view of the efficient protodesilylation procedure developed by Roush and coworkers,[24] the dimethylphenylsilylmethyl group appeared to be a perfect candidate. Most gratifyingly, when the aminonitrile epimers **12** were subjected to the Bruylants reaction with dimethylphenylsilylmethylmagnesium bromide, without prior iminium formation with silver tetrafluoroborate, an excellent level of diastereoselectivity was in fact realized (>20:1). The major isomer **13** could be isolated in 69% yield (Scheme 4).



Scheme 4 *Reagents and conditions*: (a) $Me_2PhSiCH_2MgBr$, THF (dr >20:1), SiO_2, 69%; (b) TBAF·H_2O, DMF, 80 °C, 83%; (c) H_2, Pd/C, EtOH, 6 M HCl, 74%.

After some experimentation, it was found that protodesilylation of silane **13** could be cleanly accomplished in pure DMF in the presence of TBAF to afford the *exo* methyl derivative **14** in 83% yield after silica gel purification. Concomitant deprotection of the three hydroxyl groups was then readily achieved through hydrogenolysis in acidic medium to provide (+)-hyacinthacine A_7 in 74%

yield. The synthetically derived hyacinthacine A_7 furnished ^{1}H NMR and ^{13}C NMR data consistent with those of the natural material.[25]

In conclusion, (+)-hyacinthacine A_6 and (+)-hyacinthacine A_7 have been efficiently synthesized in high enantiomeric purity from a common, late-stage intermediate. The approach, based on an asymmetric [2+2] cycloaddition of dichloroketene to a chiral enol ether, allows flexible and highly stereocontrolled introduction of each of the C-5 epimeric substituents. The approach is thus particularly well suited for the preparation of other C-5-substituted hyacinthacines, such as the hydroxybutyl hyacinthacine A_1 derivative[26] **4** (Figure 1).[27]

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synlett.

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(25) Our synthetic hyacynthacine A_7 is dextrorotatory {$[\alpha]_D$ +48}, as was Donohoe's[9b] (but not Izquierdo's[10]) with the same indicated absolute stereochemistry. Based on the reported[8] levorotation {$[\alpha]_D$ –52} of natural hyacynthacine A_7 and the dextrorotation of natural and synthetic hyacynthacine A_6, the two alkaloids, most surprisingly, would appear to belong to different enantiomeric series. Previous workers[9b] have reached the same conclusion from the rotational data.

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(27) **Experimental Procedures for Methyl Introductions (2*S*,3a*R*,4*S*,6*R*,8a*R*,8b*S*)-4-{[Dimethyl(phenyl)silyl]-methyl}-6-methyl-2-phenylhexahydro-3a*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine (10)**

To a degassed solution of aminonitriles **8** (14.7 mg, 0.035 mmol) in THF (1.0 mL) at –60 °C was added a degassed solution of LDA (1.0 M, 0.073 mL). After 15 min, MeI (0.011 mL, 0.177 mmol) was added, and the resulting solution was stirred at –60 °C for 30 min before the addition of sat. aq NH_4Cl. After being allowed to warm to r.t., the reaction mixture was processed with EtOAc to give 17 mg of crude aminonitriles **9**, which were used without further purification. To a solution of this material in anhydrous THF (0.21 mL) at 0 °C was added dropwise a solution of $LiBHEt_3$ (1.0 M in THF, 0.17 mL, 0.17 mmol). The reaction mixture was stirred for 30 min at this temperature and then quenched with H_2O and processed with EtOAc. The resulting crude product was purified by silica gel chromatography (2–5% MeOH saturated with NH_3 in EtOAc) to afford 13.0 mg (78%) of **10**: $[\alpha]_D^{21}$ –4 (*c* 1.2, $CHCl_3$). IR (film): 3065, 3022, 2950, 2915, 1660 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 0.34 (s, 3 H), 0.36 (s, 3 H), 0.95 (d, *J* = 6.3 Hz, 3 H), 0.97 (A of ABX, *J* = 14.6, 8.6 Hz, 1 H), 1.07 (B of ABX, *J* = 14.6, 6.4 Hz, 1 H), 1.48 (dddd, *J* = 11.5, 8.5, 7.6, 7.6 Hz, 1 H), 1.60 (dddd, *J* = 12.0, 7.6, 7.6, 7.6 Hz, 1 H), 1.86 (dddd, *J* = 11.5, 7.6, 6.3, 5.3 Hz, 1 H), 1.96 (dddd, *J* = 12.0, 8.5, 5.3, 5.3 Hz, 1 H), 3.05 (ddddd, *J* = 7.6, 6.3, 6.3, 6.3, 6.3 Hz, 1 H), 3.47 (ddd, *J* = 8.5, 6.4, 1.9 Hz, 1 H), 3.50 (ddd, *J* = 7.6, 5.3, 5.3 Hz, 1 H), 4.44 (dd, *J* = 6.2, 1.9 Hz, 1 H), 4.54 (dd, *J* = 6.2, 5.3 Hz, 1 H), 5.75 (s, 1 H), 7.29–7.44 (m, 6 H), 7.47–7.59 (m, 4 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = –2.4 (CH_3), 18.1 (CH_3), 20.1 (CH_2), 23.2 (CH_2), 34.7 (CH_2), 54.5 (CH), 57.9 (CH), 66.3 (CH), 81.9 (CH), 91.2 (CH), 105.5 (CH), 126.7 (CH), 127.7 (CH), 128.2 (CH), 128.7 (CH), 129.0 (CH), 133.6 (CH), 136.8 (C), 139.5 (C). ESI-MS: *m/z* = 394 [MH^+]. ESI-HRMS: *m/z* calcd for $C_{24}H_{32}NO_2Si$: 394.2197; found: 394.2194 [MH^+].

(2*S*,3a*R*,4*R*,6*S*,8a*R*,8b*S*)-4-(Benzyloxymethyl)-6-methyl-2-phenylhexahydro-4*H*-[1,3]dioxolo[4,5-*a*]pyrrolizine (14)

To a solution of pyrrolizidine **13** (15.0 mg, 0.030 mmol) in anhydrous DMF (0.30 mL) was added solid TBAF·H_2O (84 mg, 0.30 mmol), and the reaction mixture was heated at 80 °C for 16 h. An additional portion of solid TBAF·H_2O (42 mg, 0.15 mmol) was then added, and the resulting mixture was stirred at 80 °C for 8 h. After the addition of sat. aq NH_4Cl, the reaction mixture was processed with EtOAc. The resulting crude material was purified by silica gel chromatography (0–5% MeOH saturated with NH_3 in CH_2Cl_2) to afford 9.1 mg (83%) of **14**: $[\alpha]_D^{25}$ +32 (*c* 0.9, $CHCl_3$). IR (film): 3027, 2921, 2850, 1456 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.06 (d, *J* = 5.9 Hz, 3 H), 1.51 (dddd, *J* = 11.9, 9.5, 9.5, 9.5 Hz, 1 H), 1.94 (dddd, *J* = 12.8, 9.5, 9.5, 2.4 Hz, 1 H), 2.06 (dddd, *J* = 11.9, 9.5, 5.9, 2.4 Hz, 1 H), 2.22 (dddd, *J* = 12.8, 9.5, 9.5, 4.9 Hz, 1 H), 3.32 (ddddd, *J* = 9.5, 5.9, 5.9, 5.9, 5.9 Hz, 1 H), 3.38–3.47 (m, 2 H), 3.50–3.57 (m, 1 H), 3.83 (ddd, *J* = 9.5, 4.9, 4.9 Hz, 1 H), 4.52 (A of AB, *J* = 12.0 Hz, 1 H), 4.59 (B of AB, *J* = 12.0 Hz, 1 H), 4.64 (dd, *J* = 6.1, 4.9 Hz, 1 H), 4.85 (d, *J* = 6.1 Hz, 1 H), 5.77 (s, 1 H), 7.27–7.30 (m, 1 H), 7.31–7.36 (m, 4 H), 7.37–7.42 (m, 3 H), 7.44–7.50 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2 (CH_3), 22.9 (CH_2), 34.9 (CH_2), 60.6 (CH), 66.0 (CH), 67.5 (CH), 72.9 (CH_2), 73.3 (CH_2), 85.0 (CH), 87.6 (CH), 105.7 (CH), 126.8 (CH), 127.5 (CH), 128.3 (CH), 128.4 (CH), 129.4 (CH), 136.3 (C), 138.3 (C). ESI-MS: *m/z* = 366 [MH^+]. ESI-HRMS: *m/z* calcd for $C_{23}H_{28}NO_3$: 366.2064; found: 366.2069 [MH^+].

