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Total Synthesis of Hyacinthacine A_1 and 3-*epi*-Hyacinthacine A_1

Laurent Chabaud,[†] Yannick Landais,*[,†] and Philippe Renaud*[,‡]

Laboratoire de Chimie Organique et Organométallique, Université Bordeaux-I, 351, Cours de la Libération, F-33405 Talence Cedex, France, and Department of Chemistry and Biochemistry, University of Berne, Freiestrasse 3, CH-3000 Berne 9, Switzerland

y.landais@lcoo.u-bordeaux.fr; philippe.renaud@ioc.unibe.ch

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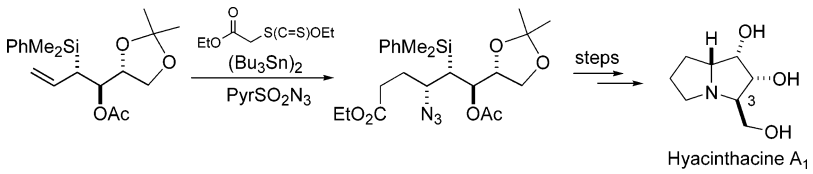
ABSTRACT

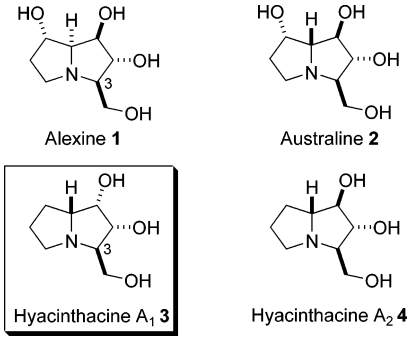


Total synthesis of hyacinthacine A_1 and its epimer at C3 is described. The synthesis includes a stereocontrolled carboazidation of a chiral allylsilane as a key step. C–Si bond oxidation and reduction of the azide, with ring-closure, complete the total synthesis, which establishes the absolute configuration of 3.

Polyhydroxylated pyrrolizidine alkaloids possessing a hydroxymethyl substituent at C3 are relatively rare in nature. Several members of this class of alkaloids, including australine **1** and alexine **2**, have been isolated from leguminosae (*Castanospermum* and *Alexa*) and exhibit promising biological activity[1] (e.g., **1** displays antiviral and anti-HIV activity).[2] More recently, Asano et al. reported the isolation, from an extract of *Muscari Armeniacum*, of hyacinthacines A_1 (**3**), A_2 (**4**), A_3, and B_3, new potent inhibitors of glycosidase.[3] The absolute configuration of hyacinthacine A_1 remains unknown. It was assigned structure **3** and was shown to be an effective inhibitor of rat intestinal lactase (IC_{50} 4.4 μM).

While several total syntheses of hyacinthacine A_2 (**4**) have been recently completed,[4] the synthesis of **3** has not been achieved to date.[5] We report here the first total synthesis of hyacinthacine A_1 and one of its stereoisomers, thus establishing the absolute configuration of the natural product. Our

Scheme 1. Structures of Polyhydroxylated Pyrrolizidines



[†] Université Bordeaux-I.
[‡] University of Berne.

(1) (a) 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**, *29*, 2487−2490. (b) Molyneux, R. J.; Benson, M.; Wong, R. Y.; Tropea, J. E.; Elbein, A. D. *J. Nat. Prod.* **1988**, *51*, 1198−1206. (c) Winchester, B.; Al Dahler, S.; Carpenter, N. C.; Cenci Di Bello, I.; Choi, S. S.; Fairbanks, A. J.; Fleet, G. W. J. *Biochem. J.* **1993**, *290*, 743−749.

(2) Taylor, D. L.; Nash, R.; Fellows, L. E.; Kang, M. S.; Tyms, A. S. *Antiviral Chem. Chemother.* **1992**, *3*, 273−277.

(3) 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*, 1−8.

(4) (a) Rambaud, L.; Compain, P.; Martin, O. R. *Tetrahedron: Asymmetry* **2001**, *12*, 1807−1809. (b) Izquierdo, I.; Plaza, M. T.; Franco, F. *Tetrahedron: Asymmetry* **2003**, *14*, 3933−3935. (c) Cardona, F.; Faggi, E.; Liguori, F.; Cacciarini, M.; Goti, A. *Tetrahedron Lett.* **2003**, *44*, 2315−2318. (d) Desvergnes, S.; Py, S.; Vallée, Y. *J. Org. Chem.* **2005**, *70*, 1459−1462.

(5) For an approach, see: Toyao, A.; Tamura, O.; Takagi, H.; Ishibashi, H. *Synlett* **2003**, 35−38.

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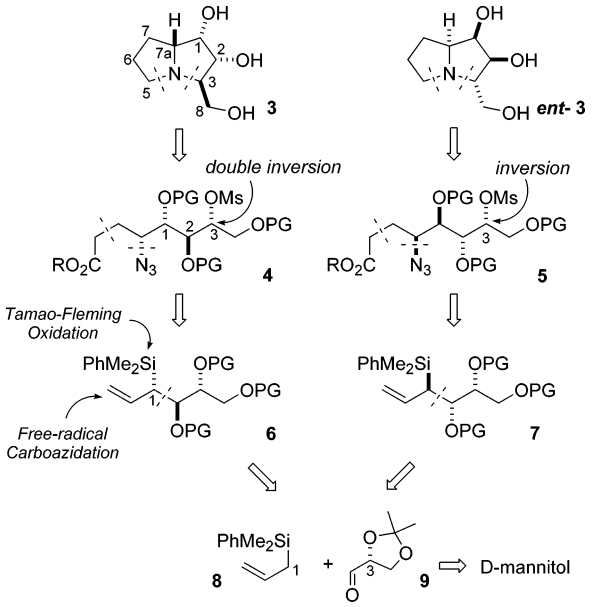
strategy is based on a free-radical carboazidation[6] of a chiral allylsilane as a key step,[7] the silicon group being used both to ensure a high level of 1,2-stereocontrol[8] and as a latent hydroxy group.[9]

As the absolute configuration of natural hyacinthacine A_1 was unknown, we envisioned two different routes starting from diastereomeric allylsilanes **6** and **7** that could lead to both enantiomers of **3** (Scheme 2). Disconnection of **3** and

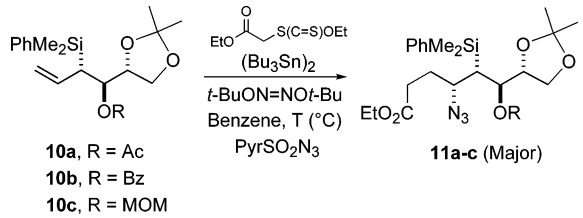
Scheme 2. Retrosynthetic Analysis



ent-**3** thus reveals that both rings should be formed late in the synthesis, with the ring closure occurring from intermediates **4** and **5**, having the four contiguous stereogenic centers correctly set up. The configuration of the C3 center would be imposed by the use of aldehyde **9**, readily available from D-mannitol.[10] Intermediates **4** and **5** would be accessible through carboazidation of allylsilanes **6** and **7**, followed by Tamao−Fleming oxidation of the $PhMe_2Si$ group with retention of configuration. Reduction of the azido group of **4** or **5** with concomitant ring closure would then lead to **3** or *ent*-**3**.[6b,c] While ring closure from mesylate **5** is expected to occur with inversion of configuration at C3, leading to *ent*-**3**, the synthesis of **3** from **4** would require a double inversion (retention) at C3. This study showed that a careful choice of the alcohol protective groups and the inversion of the C3 configuration prior to ring closure were critical for completion of the total synthesis of **3**.

The scope of the carboazidation reaction was studied using enantiomerically pure allylsilanes **10a**−**c**, easily obtained through Roush allylation of aldehyde **9**.[11] We first observed that better yields were obtained when the alcohol function β to silicon (C2) was protected. A rapid survey of the reaction conditions and variation of the protective group was thus carried out, the results of which are summarized in Table 1.

Table 1. Free-Radical Carboazidation of Allylsilanes **10a**−**c**



entry	olefin (equiv)	xanthate (equiv)	*t* (°C)	*syn*/*anti*	yield (%)[c]
1	**10a** (2)	1	80	84:16[a]	74
2	**10a** (2)	1	60	85:15[a,b]	84
3	**10a** (1)	2	60	70:30[a]	87
4	**10b** (2)	1	60	80:20[a]	30
5	**10c** (2)	1	60	61:39[a]	52

[a] Ratio estimated from ^{1}H NMR of the crude reaction mixture. [b] Ratio estimated from ^{28}Si NMR of the crude reaction mixture. [c] Isolated yield.

The acetate group afforded the best results, with the *syn*-carboazidation product **11a** obtained as the major isomer with reasonable diastereocontrol (Table 1, entries 1 and 2).[12] Interestingly, lowering the temperature led to no change in the diastereocontrol but gave consistently better yields, indicating that some of the carboazidation product may be decomposed at 80 °C (Table 1, entry 2). The reaction is generally best carried out using 2 equiv of allylsilane for 1 equiv of xanthate, the excess of allylsilane being recovered by chromatography. Reversal of the ratio also led to good yield, albeit with slightly lower diastereocontrol (Table 1, entry 3).

The use of a MOM ether (i.e., **10c**) gave modest diastereocontrol and lower yield, probably because of hydrogen abstraction on the MOM group (vide infra). The benzoate **10b**, which was difficult to isolate in pure form, also afforded a small amount of carboazidation product. Finally, the use of 3-pyridylsulfonyl azide ($PyrSO_2N_3$) instead of $PhSO_2N_3$ made the purification of the products easier and provided higher yields.[13] The study was next extended to the carboazidation of the acetate-protected *anti*/*syn* allylsilane **12**. Surprisingly, reaction under the above optimized conditions led to azide **14** as a single isomer (stereochemistry not determined at the anomeric center) and no trace of the

(6) (a) Ollivier, C.; Renaud, P. *J. Am. Chem. Soc.* **2001**, *123*, 4717−4727. (b) Ollivier, C.; Renaud, P.; Penchaud, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 3460−3462. (c) Panchaud, P.; Ollivier, C.; Renaud, P.; Zigmantas, S. *J. Org. Chem.* **2004**, *69*, 2755−2759.

(7) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2002**, *4*, 4257−4260.

(8) Chabaud, L.; James, P.; Landais, Y. *Eur. J. Org. Chem.* **2004**, 3173−3199.

(9) (a) Fleming, I. *Chemtracts: Org. Chem.* **1996**, 1−64. (b) Landais, Y.; Jones, G. *Tetrahedron* **1996**, *52*, 7599−7662. (c) Tamao, K. In *Advances in Silicon Chemistry*; Jai Press Inc.: Greenwich, 1996; Vol. 3, pp 1−62.

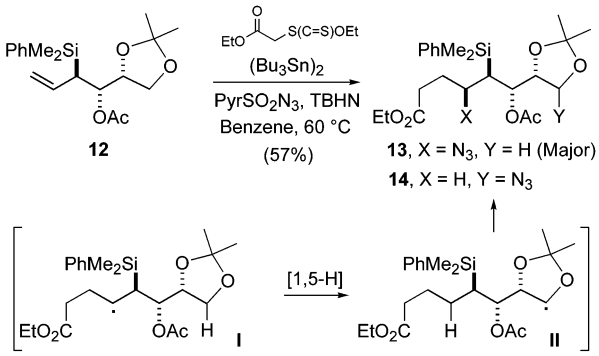
(10) Schmid, C. R.; Bryant, J. D. *Org. Synth.* **1995**, *72*, 6−13.

(11) Roush, W. R.; Grover, P. T. *Tetrahedron* **1992**, *48*, 1981−1998.

(12) Relative configuration of our products were determined through a stereospecific fluoride-mediated β-elimination of the β-silyl azide; see: (a) Masterson, D. S.; Porter, N. D. *Org. Lett.* **2002**, *4*, 4253−4256. (b) Chabaud, L.; Landais, Y. *Tetrahedron Lett.* **2003**, *44*, 6995−6998.

(13) Panchaud, P.; Renaud, P. *Adv. Synth. Catal.* **2004**, *34*, 925−928.

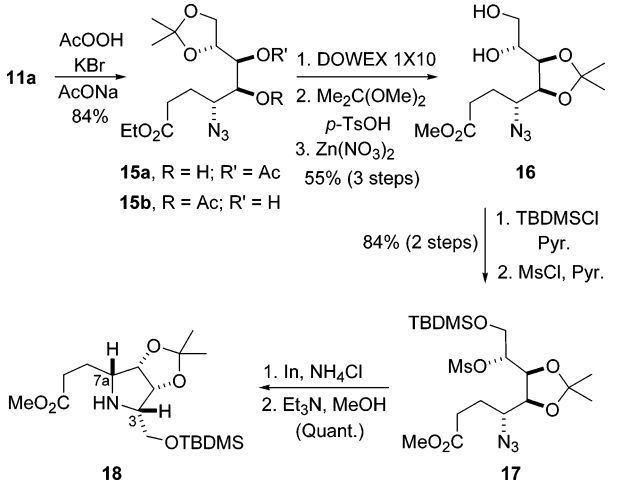
Scheme 3. Carboazidation of Allylsilane **12**; 1,5-Hydrogen Atom Transfer



β-azidosilane **13** (Scheme 3). Azide **14** probably results from a 1,5-hydrogen atom transfer,[14] occurring after addition of the xanthate onto the allylsilane. The radical **I**, β to the silicon group, is then suitably located to abstract a hydrogen on the dioxolane ring to generate a more stable radical **II**, which then reacts with $PyrSO_2N_3$ to produce **14**. Increasing the amount of sulfonyl azide up to 10 equiv finally led to a 7:3 **13/14** ratio (^{28}Si NMR), with β-azidosilane **13** formed in 57% as an inseparable 8:2 mixture of *syn*/*anti* diastereomers. Conformational effects are likely critical and may explain the different behavior of allylsilane **12** as compared to its isomer **10a** (vide supra). As a comparison, treatment of the triacetate analogue of **12** under similar carboazidation conditions led to the expected β-azidosilane in 80% yield and a 73:27 *syn*/*anti* ratio.

On the basis of these results, the total synthesis was pursued with the *syn*-azidosilane **11a**, possessing the four required contiguous stereogenic centers. Installation of the OH group at C1 was carried out through the Tamao−Fleming oxidation of the silicon group. While this oxidation appeared challenging at first because of the presence of a β-acetoxysilane and a β-azidosilane, prone to elimination, the oxidation finally occurred smoothly using a buffered medium (AcONa) (Scheme 4).[15] The alcohol was obtained in good yield as a mixture of acetate **15a,b** as a result of 1,2-acyl migration. The acetates were saponified using a DOWEX 1-X-10 ion-exchange resin, leading to a diol that was directly protected as an acetonide. Transesterification of the ethyl ester into a methyl ester occurred concomitantly. The selective deprotection of the bis-acetonide required much effort, and the most satisfying conditions were those employing $Zn(NO_3)_2$ at 50 °C, which provided diol **16** in a corrected 75% yield (56% conversion).[16] Protection of the primary alcohol as a *tert*-butyldimethylsilyl (TBDMS) ether, followed by mesylation, then provided the intermediate **17**. This was

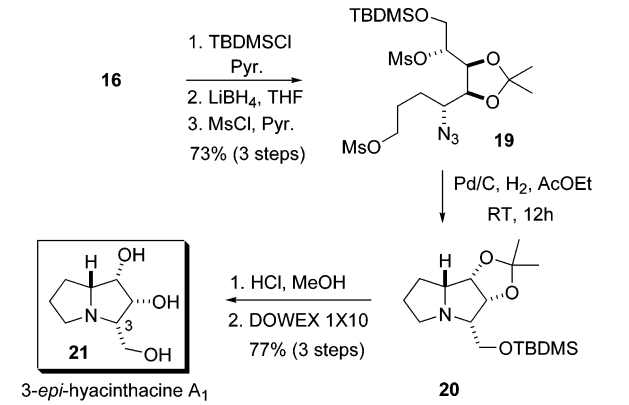
Scheme 4. Approach toward 3-*epi*-Hyacinthacine A_1



used to test the azide reduction step, which was expected to provide the pyrrolizidine skeleton in a single step through cyclization-lactamization. Reduction of the azide using indium[17] led efficiently to the monocylic amine **18**, which resisted further lactamization. As expected, the formation of the pyrrolidine ring had occurred with inversion of configuration at C3. Attempts to carry out the second ring closure unfortunately failed, whatever the conditions (vide infra). Steric interactions between the ester function and the CH_2-OTBDMS group (*endo*) and/or the acetonide probably prevent the attack of the amino group on the ester function in a 5-*exo*-*trig* fashion.

It was then decided to carry out cyclization using instead a 5-*exo*-*tet* process. The ester function in **16** was thus reduced into an alcohol and both hydroxyl groups converted into the bis-mesylate **19** (Scheme 5). In contrast with the cyclization

Scheme 5. Synthesis of 3-*epi*-Hyacinthacine A_1, **21**



of **17**, reduction of the azido group in **19** with indium or PPh_3-H_2O[18] led to poor results. Cyclization was finally

(14) For a review on hydrogen atom abstraction, see: Feray, L.; Kuznetsov, N.; Renaud, P. In *Radicals in Organic Synthesis*; Renaud, P., Sibi, M. P., Eds; Wiley-VCH: Weinheim, 2001; Vol. 2, p 246.

(15) (a) Fleming, I.; Henning, R.; Parker, D. C.; Plaut, H. E.; Sanderson, P. E. J. *J. Chem. Soc., Perkin Trans. 1* **1995**, 317−337. (b) Panek, J. S.; Zhang, J. *J. Org. Chem.* **1993**, *58*, 294−296. The use of $Hg(OAc)_2$/AcOOH conditions led to a complex mixture.

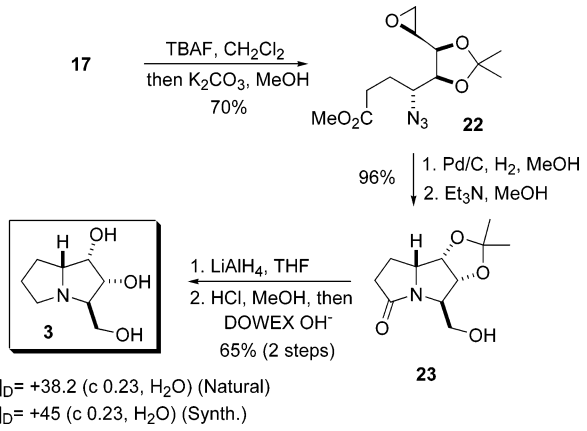
(16) Vijayasaradhi, S.; Singh, J.; Aidhen, I. J. *Synlett* **2000**, 110−112.

(17) Vidyasagar Reddy, G.; Venkat Rao, G.; Iyengar, D. S. *Tetrahedron Lett.* **1999**, *40*, 3937−3938.

successfully carried out using H_2/Pd−C,[19] leading to the tricyclic system **20**, from which acetonide and TBDMS groups were then removed under acidic conditions. Purification of the chlorhydrate through a basic DOWEX column eventually provided 3-*epi*-hyacinthacine A_1 (**21**), thus obtained in 13 steps and 12% overall yield from allylsilane **8**.

As mentioned above, the synthesis of natural hyacinthacine A_1 using this strategy entailed that a double inversion at C3 was performed on the carboazidation product **11a** or one of its derivatives (i.e., **16** or **17**). This was eventually achieved by converting the mesylate **17** into the corresponding epoxide **22** (Scheme 6).[20] Treatment of **17** with a fluoride source led

Scheme 6. Synthesis of Hyacinthacine A_1, **3**



to the alcohol deprotection which was followed by the cyclization in the presence of a base,[21] providing **22** with inversion of configuration at C3. Reduction of the azide with H_2−Pd/C then afforded the amine, which on treatment with Et_3N led to **23** by a subsequent cyclization-lactamization. This result contrasts with the behavior of **17** (Scheme 4) and indicates that the steric hindrance of the CH_2OR group (*exo* in **23**) and the relative configuration at C3 influence the rate of lactamization. It is also noticeable that no trace of 6-*endo* product could be detected. Reduction of the lactam using $LiAlH_4$, followed by deprotection as above provided hyacinthacine A_1 (**3**), the optical rotation of which matches that of the natural product, demonstrating that the structure attributed by Asano et al. to natural **3** was correct. Compound **3** was thus obtained in 13 steps and 8% overall yield from allylsilane **8**.

In summary, we report here on the total synthesis of hyacinthacine A_1 (**3**), a potent inhibitor of glycosidase, and one of its epimers **21**, thus establishing the absolute configuration of the natural product. In the course of this study, we also faced for the first time a competitive [1,5]-hydrogen transfer in carboazidation reactions of olefins. These results underline the influence of conformational effects in free-radical transformation and more particularly in this carboazidation process. It may also be added that this approach is not restricted to pyrrolizidines having an *anti* C1/C2 relative configuration as the *syn*-isomers are also available, using an alternative approach.[22] Analogues of **3** may be thus at hand by simply changing the relative configuration of the starting allylsilane **6** or **7** (Scheme 2). Finally, this work further demonstrates the utility of the silyl group, first in the control of the stereochemistry in radical processes[8,23] and as a masked hydroxy group.

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Supporting Information Available: Representative experimental procedures including product characterization. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) Vaultier, M.; Knouzi, N.; Carrié, R. *Tetrahedron Lett.* **1983**, *24*, 763−764.
(19) Cossy, J.; Willis, C.; Bellosta, V.; Saint-Jalmes, L. *Synthesis* **2002**, 951−957.
(20) Molander, G. A.; Swallow, S. *J. Org. Chem.* **1994**, *59*, 7148−7151.
(21) Formation of the epoxide occurs spontaneously after deprotection and is completed through addition of K_2CO_3.
(22) (a) Yamamoto, Y.; Saito, Y.; Maruyama, K. *J. Chem. Soc., Chem. Commun.* **1982**, 1326−1328. (b) Yamamoto, Y.; Yatagai, H.; Ishihara, Y.; Maeda, N.; Maruyama, K. *Tetrahedron* **1984**, *40*, 2239−2246.
(23) Landais, Y. *C. R. Acad. Sci., Ser. IIc: Chem.* **2005**, *8*, 823−832.