JOC*Article*

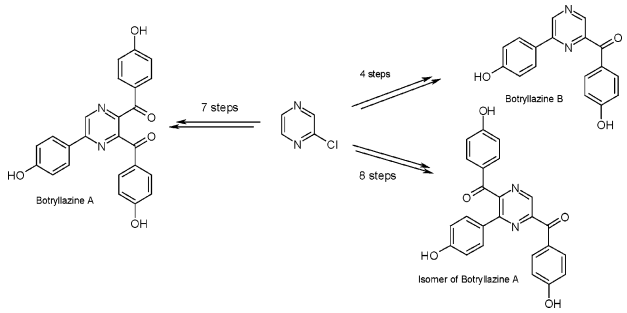
Synthesis of Pyrazine Alcaloids from *Botryllus leachi*. Diazines 43

Frédéric Buron, Nelly Plé, Alain Turck,* and Guy Queguiner

IRCOF, Laboratoire de Chimie Organique Fine et Hétérocyclique, UMR 6014, INSA, B.P. 08, 76131 Mont St. Aignan Cedex, France

alain.turck@insa-rouen.fr

Received December 13, 2004



Regioselective metalation of pyrazines and cross-coupling reactions provides an easy access to botryllazines A and B and to an isomer of botryllazine A with good yields from chloropyrazine.

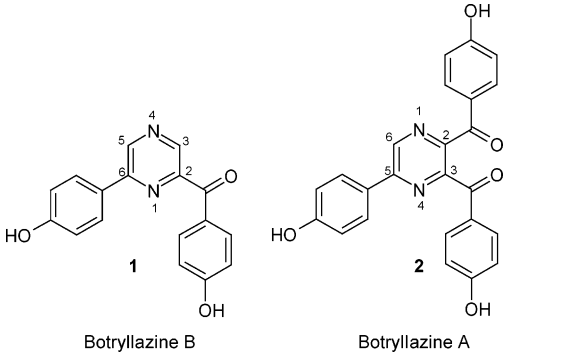
Introduction

Ascidians, which are small marine animals, are present in all the seas and are the source of naturally occurring alkaloids. In 1999, Duran et al.[1] isolated two pyrazine alkaloids from *Botryllus leachi*: botryllazines A and B (Scheme 1). These compounds exhibited cytotoxicity against human tumor cells. This antineoplasmic activity prompted us to perform a synthesis of these two compounds. In the course of this work, a synthesis of botryllazine B was described by S. Mahboobi[2] starting from 4-methoxyacetophenone by building of the pyrazine ring; the overall yield was 11%. Our syntheses are based on the regioselective functionalization of the pyrazine ring by metalation and cross-coupling reactions starting from commercial chloropyrazine **3**.

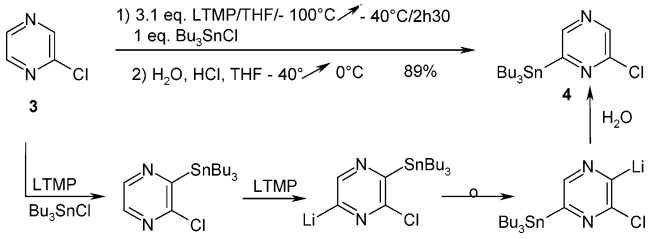
Results and Discussion

Synthesis of Botryllazine B. In our laboratory, F. Toudic[3] performed the synthesis of 2-fluoro-6-tributylstannylpyrazine by a non-ortho-directed metalation of fluoropyrazine. The same experimental procedure was used with chloropyrazine **3** and afforded 2-chloro-6-tributylstannylpyrazine **4** with an 89% yield (Scheme 2).

SCHEME 1



SCHEME 2



It was demonstrated that the key intermediate was 2-chloro-3-tributylstannylpyrazine, which was again metalated and isomerized quickly to 2-chloro-3-lithio-6-tributylstannylpyrazine in the presence of an excess of LTMP affording **4** after hydrolysis.

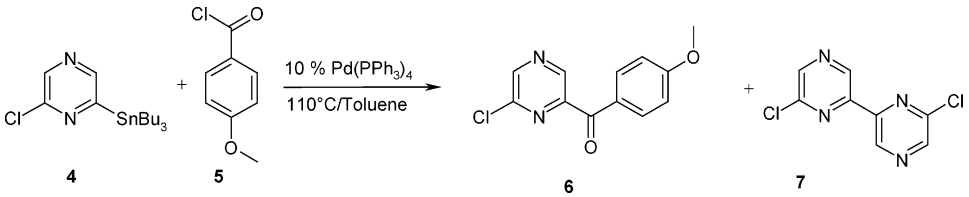
(1) (a) Duran, R.; Zubia, E.; Ortega, M. J.; Naranjo, S.; Salva, J. *Tetrahedron* **1999**, *55*, 13225. (b) Zubia, F.; Ortega, M. J.; Salva, J. *Ciencias Marinas* **2003**, *29*, 251.

(2) Mahboobi, S.; Sellmer, A.; Burgemeister, T.; Lyssenko, A.; Shollmeyer, D. *Monatsch. Chem.* **2004**, *135*, 333.

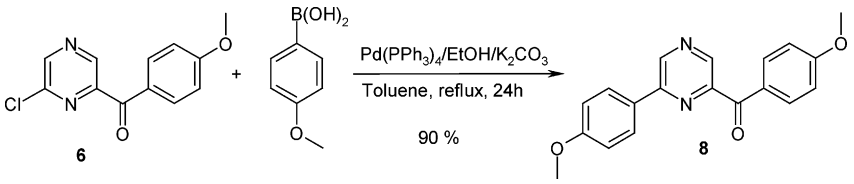
(3) Toudic, F.; Heynderickx, A.; Plé, N.; Turck, A.; Queguiner, G. *Tetrahedron* **2003**, *59*, 6375.

10.1021/jo0478196 CCC: $30.25
Published on Web 02/25/2005

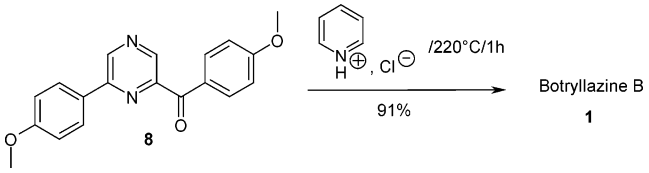
SCHEME 3



SCHEME 4



SCHEME 5



A Stille cross coupling reaction was performed with **4** and 4-methoxybenzoyl chloride **5**. We first obtained a mixture of products **6** and **7** with a 64% yield (process A); product **7** resulted from the homocoupling of **4** (Scheme 3).

To solve this problem, the order of introduction of the reactants was modified (process B). *p*-Methoxy-benzoyl chloride **5** was mixed first with the palladium catalyst, and then the pyrazine **4** was introduced. Using this procedure allowed the formation of **7** to be avoided, and product **6** was obtained with a 70% yield. This product was cross-coupled again with 4-methoxyphenyl boronic acid following the Suzuki procedure to give compound **8** with good yield (Scheme 4).

The last step was the cleavage of the methoxy group; the usual reagents (HI, HBr, BBr_3) were tested without success: a mixture of uncleaved, monocleaved, and dicleaved products was obtained. The method of Royer[4] with pyridinium hydrochloride afforded botryllazine B with excellent yield (Scheme 5).

In summary, the synthesis of botryllazine B was performed in four steps from 2-chloropyrazine with an overall yield of 51%.

Synthesis of Botryllazine A. The easy access to compound **8** prompted us to choose it as the starting material for synthesis of botryllazine A. The ketone was protected as dioxolane; then, the product was metalated in order to obtain a metalation ortho to the dioxolane (Scheme 6, Table 1). A metalation with dioxolane as an ortho directing group was recently reported with derivatives of acetophenone.[5]

TABLE 1. Metalation of 8 Followed by Reaction with Anisaldehyde[a]

entry	base	equiv	time	temp	yield	ratio **10/11**
1	LTMP	2.1	0.5 h	−75°C		
2	LTMP	3.1	0.5 h	−75°C	70%	70/30
3	LTMP	3.1	0.5 h	−100°C		
4	LTMP	3.1	in situ trapping	−75°C	64%	70/30
5	LDA	3.1	0.75 h	−75°C		

[a] In the case of entries 1, 3, and 5, only the starting material was recovered.

A 3-fold excess of LTMP was necessary to achieve the metalation. The need for an excess of LTMP is due to the chelating properties of the methoxy groups.[6] The metalation was not regioselective, and the major isomer was not the useful one.

It was then attempted to slow the metalation rate ortho to the *p*-methoxyphenyl group by replacement of the hydrogen by a deuterium atom using the isotopic effect. This procedure was recently used by Y. Fort[7] et al. The deuterium atom was regioselectively introduced ortho to the chlorine atom of **12** by metalation followed by reaction with EtOD (Scheme 7). Product **13** was cross-coupled as before to afford the deuterated compound **14**.

The metalation of compound **14** gave a result very close to the metalation of the undeuterated compound **9**, a 75/25 mixture of the two isomers **10** and **11**. It must be noted that during the metalation process, the deuterium atom was replaced by a hydrogen and that compound **11** was actually recovered without the deuterium atom present in **14**. This result indicated clearly that the metalation reaction was under thermodynamic control and that the main factor was the relative stability of the lithio derivatives. A PM3/Li[8] calculation of the formation energies of the two lithio derivatives gave the following values (Scheme 8). Formation energies of the two isomers are in agreement with the experimental results.

Another solution for solving the regioselectivity problem would be the blocking of the 3 position with a

(4) (a) Royer, R.; Buisson, J.; Demerseman, P.; Chentin, A. *Bull. Soc. Chim. Fr.* **1970**, *10*, 3647. (b) Royer, R.; Demerseman, P. *Bull. Soc. Chim. Fr.* **1968**, *6*, 2634.

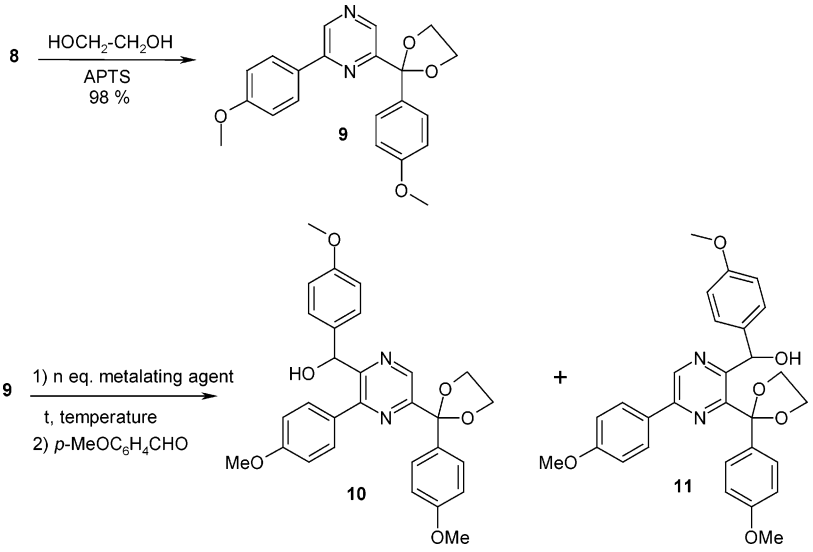
(5) Lukács, G.; Porcs-Makkay, M.; Simig, G. *Tetrahedron Lett.* **2003**, *44*, 3211.

(6) Turck, A.; Trohay, D.; Mojovic, L.; Plé, N.; Queguiner, G., *J. Organomet. Chem.* **1991**, *412*, 301.

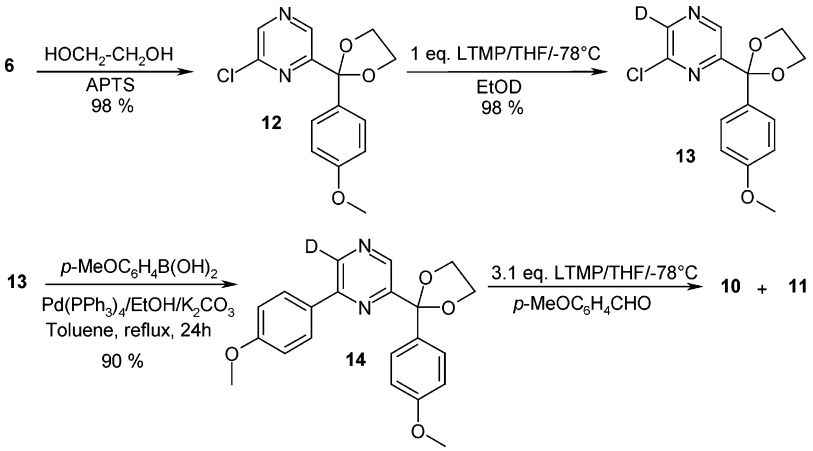
(7) Gros, P.; Choppin, S.; Fort, Y. *J. Org. Chem.* **2003**, *68*, 2243.

(8) Anders, E.; Koch, R.; Freunscht, P. *J. Comput. Chem.* **1993**, *14*, 1301.

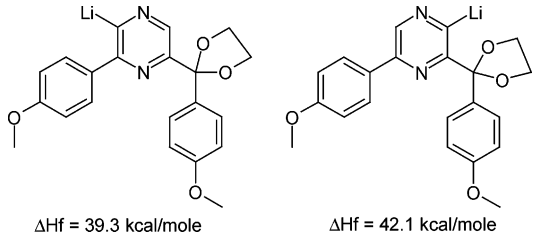
SCHEME 6



SCHEME 7



SCHEME 8



removable group. In this approach, a trimethylsilyl group was introduced at position 3 by a regioselective metalation of **12** followed by reaction with trimethylchlorosilane, affording compound **15**.

The metalation of **15** did not afford the expected product, and the desilylated compound **12** was recovered. We supposed that the desilylation reaction could be favored by the environment of the chlorine atom; we therefore performed the cross-coupling reaction with *p*-methoxyphenyl boronic acid, affording compound **16**, and then the metalation was performed (Scheme 9).

As before, the metalation afforded the desilylated product **9** along with starting material. Taking into account the failure of the blocking of position 3 by deuterium or trimethylsilyl, another route was tested. This route was based on a nucleophilic substitution of the 2-chlorine atom in order to introduce the second *p*-methoxy-benzoyl group on the diazine ring (Scheme 10).

Products **20** and **21** were obtained in three steps from commercial 2,6-dichloropyrazine **17** with good yields. The nucleophilic substitution of the 6-chlorine atom was tested with the lithiated dithiane[9] **22**, the lithiated nitrile[10] **23**, and the *p*-methoxybenzaldehyde in the presence of imidazolium salts (Miyashita reaction)[11] (Scheme 11). Despite numerous experiments, the substitution failed: the starting material was recovered along with a large amount of tar.

Although all the strategies attempting to access botryllazine A have failed, it was nevertheless possible to access to an isomer of this compound starting from the disubstituted pyrazine **12** (Scheme 12).

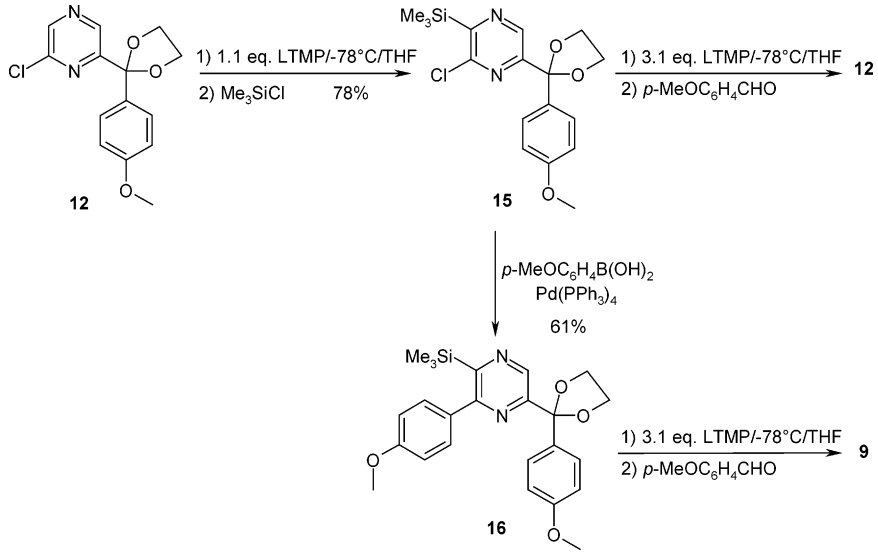
The metalation of **12** was completely regioselective ortho to the chlorine atom with good yield (82%), and

(9) Corey, E.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1965**, *4*, 1075.

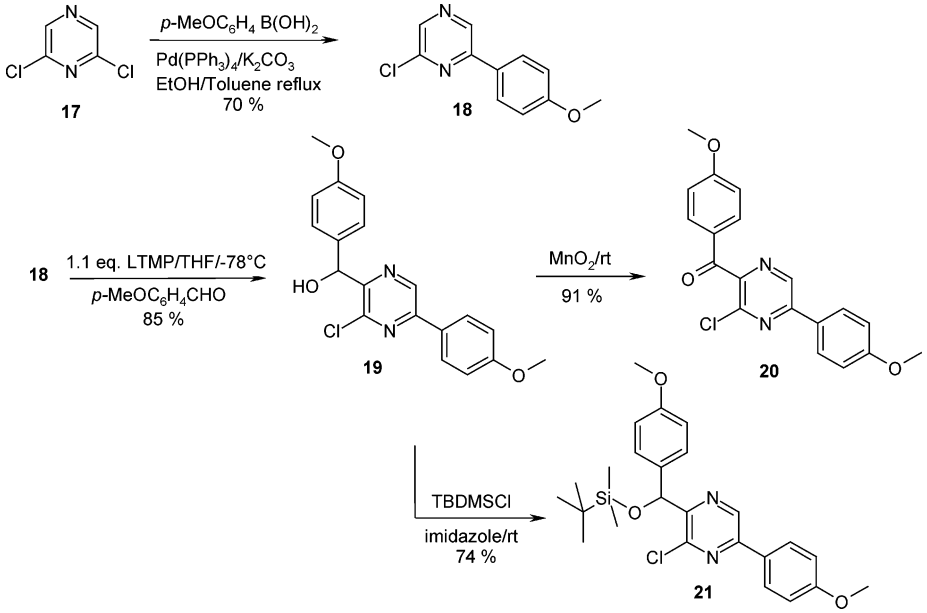
(10) Yamanaka, H.; Ohba, S. *Heterocycles* **1990**, *31*, 895.

(11) (a) Miyashita, A.; Obae, K.; Suzuki, Y.; Oishi, E.; Iwamoto, K.; Higashino, T. *Heterocycles* **1997**, *45*, 2159. (b) Miyashita, A.; Suzuki, Y.; Ohta, K.; Iwamoto, K.; Higashino, T. *Heterocycles* **1998**, *47*, 407. (c) Miyashita, A.; Matsuda, H.; Suzuki, Y.; Iwamoto, K.-i.; Higashino, T. *Chem. Pharm. Bull.* **1994**, *42*, 2107.

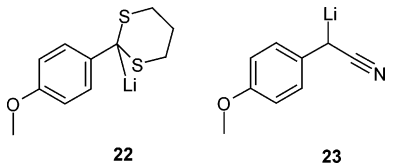
SCHEME 9



SCHEME 10



SCHEME 11

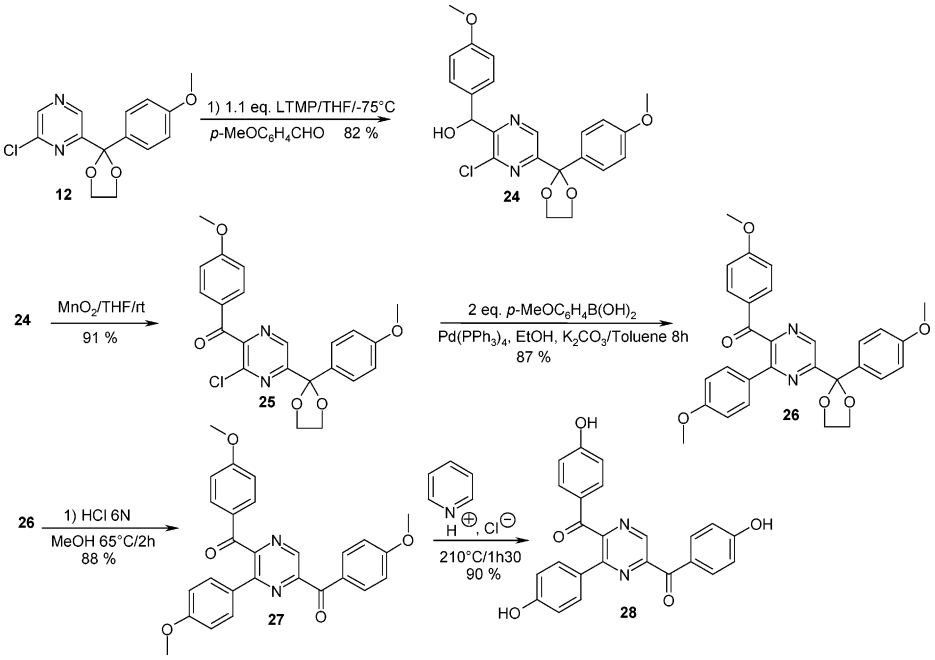


subsequent oxidation of **24** afforded **25** (91% yield). A Suzuki cross coupling afforded **26** (87%); the deprotection of the keto group was performed with hydrochloric acid in methanol (88%), and the final cleavage of the three methoxy groups was performed with pyridinium hydrochloride (90%). Compound **28**, an isomer of botryllazine A, was prepared in five steps from **12** with an overall yield of 51.5% or in eight steps from commercial chloropyrazine with a 31% yield.

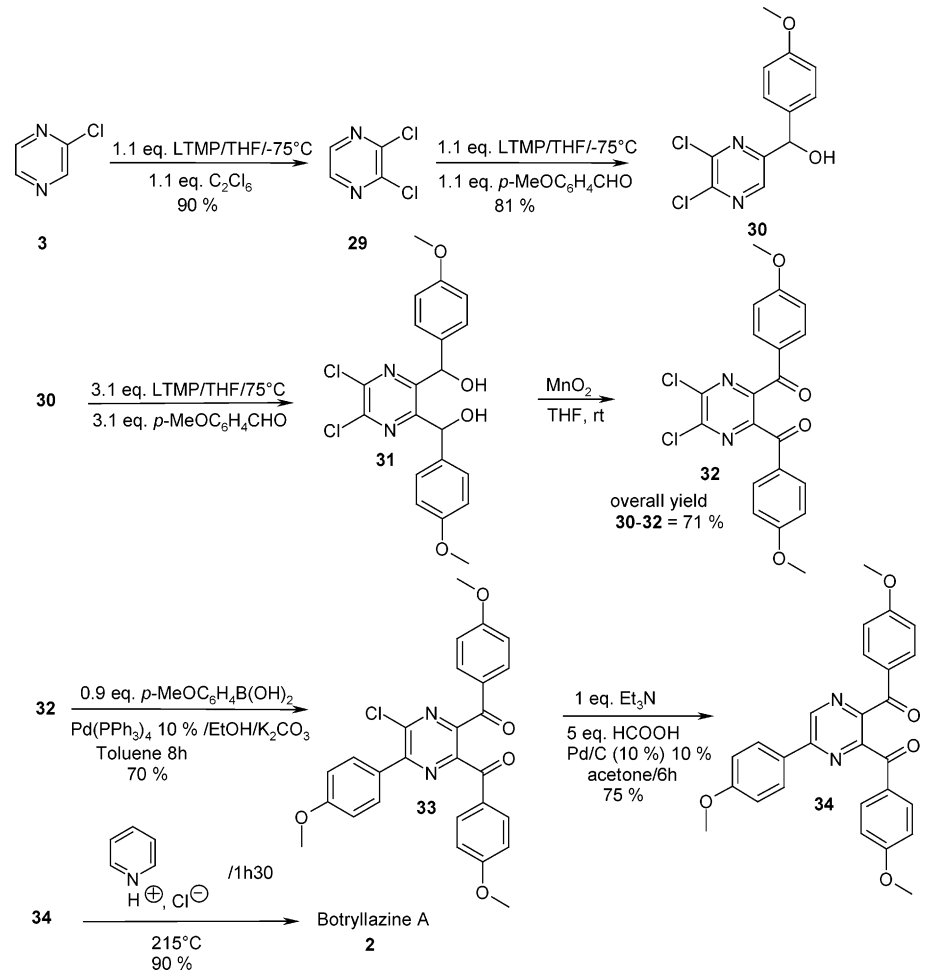
Another route to botryllazine A was then tested. This route presented no regioselectivity problem (Scheme 13). Two main syntheses of 2,3-dichloropyrazine **29** were described in the literature: either by chlorination of chloropyrazine **3**[12] or 2-chloro-pyrazine *N*-oxide[13] or by reaction of 2,3-dihydroxypyrazine[14] with phosphorus oxychloride. The use of the metalation reaction of **3** followed by the reaction with C_2Cl_6 was a new route and gave **29** with an excellent yield (90%). This was followed by two successive metalation reactions followed by reaction with *p*-methoxybenzaldehyde: the first with 1 equiv of LTMP affording **30** with good yield (81%), and the second with 3.1 equiv of LTMP afforded the tetrasubstituted pyrazine **31**. The crude product was oxidized by manganese dioxide, and the diketone **32** was obtained with a good yield from **30** (71%). A Suzuki cross-coupling reaction with the *p*-methoxyphenyl boronic acid gave **33** with a 70% yield. The reduction of the last chlorine atom was

(12) Okafor, C. O. *J. Heterocycl. Chem.* **1981**, *18*, 405.
(13) Sato, N.; Fujii, M. *J. Heterocycl. Chem.* **1994**, *31*, 1177.
(14) Palamidessi, G.; Bonanomi, M. *Edizione Scientifica* **1966**, *21*, 799.

SCHEME 12



SCHEME 13



performed with a mixture of formic acid and triethylamine catalyzed by palladium leading to **34** in 75% yield. The cleavage of the methoxy groups was performed with pyridinium hydrochloride[4] at 215 °C. Botryllazine A was obtained in seven steps from commercial chloropyrazine with an overall yield of 24.5%.

In conclusion, we have prepared two botryllazines A and B and an isomer of A in a few steps and with good overall yields from commercial chloropyrazine. These syntheses, which allow preparation of large quantities of these compounds, will help to advance the evaluation of their potential as drugs. This is currently under investigation in a laboratory of Artois University.[15]

Supporting Information Available: Experimental procedures and product characterization for new compounds and selected ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

JO0478196

(15) LBHE EA 2465, Faculté des Sciences de Lens, Pr P. Martin, SP18, 62307 Lens, France.