Natural Product Synthesis

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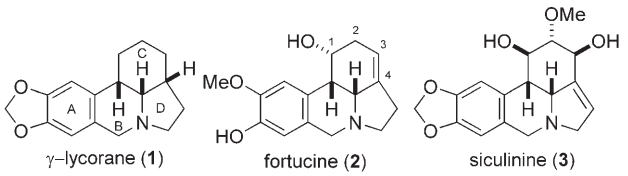
The Total Synthesis of (±)-Fortucine and a Revision of the Structure of Kirkine**

*Aurélien Biechy, Shuji Hachisu, Béatrice Quiclet-Sire, Louis Ricard, and Samir Z. Zard**

In memory of Charles Mioskowski

Lycorine alkaloids are isolated from the Amaryllidaceae species of plants,[1] and their medicinal value has an old and rich history dating back to ancient Greece.[2] Members of the lycorine alkaloids possess antineoplastic, antimitotic, insect antifeedant, and antiviral activities; they also inhibit growth and cell division in higher plants, protein and DNA synthesis in murine cells, and in vivo growth of a murine transplantable ascite tumor.[3]

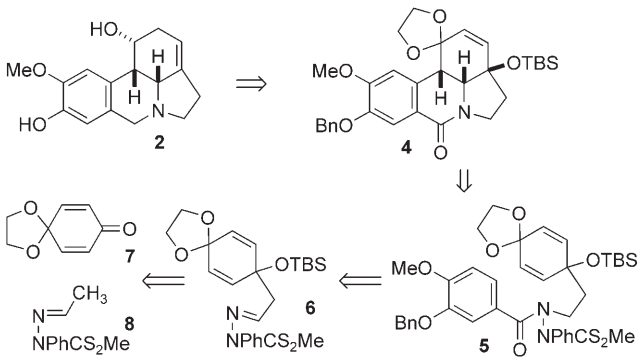
The tetracyclic pyrrolo[*d*,*e*]phenanthridine (galanthan) framework that characterizes the lycorine alkaloids has been the subject of intense synthetic scrutiny ever since the structure of lycorine itself was established in 1955.[4] While the great majority of the these alkaloids have a *trans* B/C-ring junction, there are a few compounds with a *cis* B/C-ring junction; for example, γ-lycorane (**1**), fortucine (**2**), and siculinine (**3**; Scheme 1).[3a,5]



Scheme 1. Lycorine-type alkaloids.

Fortucine (**2**) was isolated from the Fortune variety of narcissus by Tokhtabaeva et al. in 1987 [5a] A few years later, and unaware of the earlier work, Bastida et al.[5b] isolated from *Crinum kirkii*, a common grassland plant of East Africa used as a purgative, a rat poison, and a treatment for sores,[6] a substance they called kirkine and for which they attributed the same structure **2**. The reported NMR spectra showed some discrepancies between the two compounds, even if the description given for the spectrum of fortucine was incomplete and could be subject to confusion. We therefore embarked on a total synthesis of structure **2** to clarify the matter on one hand, and on the other, to provide sufficient quantities to explore more broadly the biological activity profile. Our study would also serve to establish a general strategy to access galanthan frameworks with a *cis* B/C-ring junction.

Our synthetic approach to structure **2**, henceforth called fortucine, is based on a radical cascade process (**5**→**4**) that is initiated by the generation of a nitrogen-centered (amidyl) radical, which undergoes cyclization onto the alkene followed by an oxidative cyclization to afford the aromatic ring (Scheme 2). If successful, this cascade process would simultaneously form rings B and D in one step. Furthermore, it was



Scheme 2. Retrosynthetic analysis of fortucine (**2**). Bn = benzyl, TBS = *tert*-butyldimethylsilyl.

hoped that the cyclizations would be stereoselective, to furnish the requisite *cis* B/C-ring junction, and regioselective, to give the *para* (as opposed to *ortho*) cyclized product with respect to the benzyloxy group. The key precursor would be constructed by the union of *p*-benzoquinone ethylene monoketal (**7**)[7] with the azaenolate of hydrazone **8**[8]. It is worth noting the convergent manner by which rings A and C are appended upon hydrazone **8**, which in turn provides the foundation of ring D.

The synthesis started by trapping the azaenolate derived from hydrazone **8** (3 equiv) by treatment with LDA (3 equiv) and *p*-monoketal **7** (1 equiv) to give alcohol **9** in quantitative yield (Scheme 3). Pleasingly, the desired 1,2-addition occurred exclusively without formation of the undesired 1,4-adduct. Furthermore, the efficiency of this process with respect to hydrazone **8** was surprising, because cyclization of

[*] A. Biechy, Dr. S. Hachisu, Dr. B. Quiclet-Sire, Prof. S. Z. Zard
Laboratoire de Synthèse Organique associé au CNRS
Ecole Polytechnique
Route de Saclay, 91128 Palaiseau (France)
Fax: (+33) 1-6933-5972
E-mail: zard@dcso.polytechnique.fr
Dr. L. Ricard
Laboratoire "Hétéroéléments et Coordination"
Ecole Polytechnique
Route de Saclay, 91128 Palaiseau (France)

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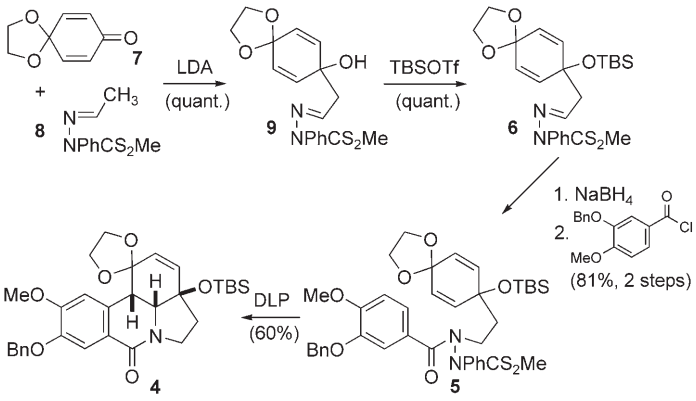


Scheme 3. Synthesis of the intermediate pentacycle **4**. LDA = lithium diisopropylamide, Tf = trifluoromethanesulfonyl, DLP = 1,2-dichloroethane with lauroyl peroxide.

the azaenolate onto the thiocarbonyl group was feared to cause major difficulties. The azaenolate of **8** was a relatively stable species at −78 °C that could be trapped by a variety of α,β-unsaturated ketones. These coupled products could in principle be used to construct dihydropyrroles via iminyl radicals,[9] and galanthan frameworks via amidyl radicals[10] through cyclizations onto neighboring unsaturated moieties.

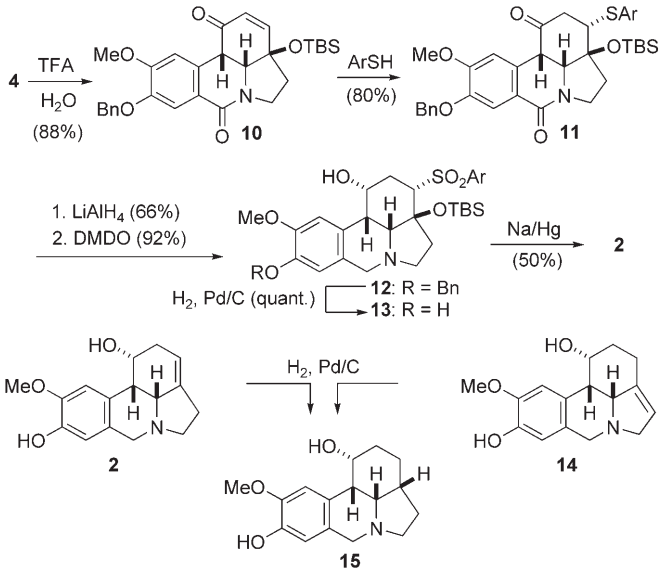
At this point it proved necessary to protect alcohol **9** as the silyl ether by treatment with TBSOTf. Attempts were made to directly transform alcohol **9** into the radical precursor **5** without introduction of a protecting group, but the instability of the free diallylic tertiary alcohol made it impossible to execute the necessary benzoylation reaction.

Hydrazone **6** was converted into radical precursor **5** by reduction with $NaBH_4$ followed by immediate acylation, of the somewhat unstable intermediate hydrazide, with 3-benzyloxy-4-methoxybenzoyl chloride to give amidyl radical precursor **5**. Treatment of **5** in refluxing 1,2-dichloroethane with lauroyl peroxide (1.4 equiv) effected the radical cascade to ultimately give pentacycle **4** in 60% yield (Scheme 3).[10] To our delight, the cascade process had occurred both stereoselectively and regioselectively to give **4** as the major product. Isomers arising from the *trans* B/C-ring junction were not observed, and the desired regioisomer was formed in a 14:1 ratio (*para*/*ortho* with respect to the benzyloxy group). The all-*cis* cyclization is inherent to this type of skeleton,[10] and the steric clash between the ethyleneketal and benzyloxy functionalities disfavors the *ortho* regiochemistry.

Interestingly, hydrazone **8** is a synthetic building block capable of reacting through ionic and radical pathways on each of its termini. The efficiency of the radical cascade to produce densely functionalized pentacycle **4** in five steps is remarkable. The structural diversity of lycorine-type alkaloids generally originates from functional groups located on ring C. The strategic positioning of the alkene, the protected ketone, and the protected alcohol in **4** can potentially be deployed to target other complex members of the lycorine family.

The remaining major task at hand was to carry out a reductive cleavage of the allylic silyl ether in **4** with concomitant migration of the double bond ($\Delta_{2,3} \rightarrow \Delta_{3,4}$), and the creation of an axial alcohol at C1. Thus, the protected ketone in **4** was unmasked to give enone **10** in 88% yield by treatment with TFA/H_2O (Scheme 4). All our efforts to induce reductive elimination of the TBS group failed and attempts to replace the TBS motif with better leaving groups were frustrated by the reactivity of the free alcohol.

In contrast, Michael addition of 2-methoxythiophenol (ArSH; Scheme 4) onto enone **10** gave thioether **11** as one diastereoisomer in 80% yield, which was subsequently treated with $LiAlH_4$ to reduce both the amide and the ketone to give the tertiary amine and alcohol groups, respectively. As expected, reduction of the ketone occurred stereoselectively from the convex face to exclusively deliver the axial alcohol. Oxidation of the sulfide group with DMDO (in the presence of TFA to protect the tertiary amine) furnished sulfone **12** in 92% yield. Hydrogenolysis over Pd/C quantitatively unmasked phenol **13**, which was subjected to Julia-type olefination using 6% Na/Hg amalgam to finally give the target molecule fortucine (**2**) in 50% yield. Some material arising from desulfonylation without elimination of the TBS group was observed in the crude product mixture, and this explains the modest yield in the last step.



Scheme 4. Synthesis of fortucine (**2**) and revision of the structure of kirkine. TFA = trifluoroacetic acid, DMDO = 2,2-dimethyldioxirane, ArSH = 2-methoxythiophenol.

Our synthetic final product was unambiguously confirmed by X-ray crystallography as having structure **2** (racemic). The NMR spectrum of our product was in accord with the data of Tokhtabaeva et al. but not with those of Bastida et al. Indeed, an authentic sample of kirkine, kindly supplied by Prof. Bastida, proved different from our synthetic material (by TLC and NMR spectroscopy). Interestingly, certain parts of the ^{1}H NMR spectrum in our case were ill resolved, apparently due to slow conformational changes in ring C as indicated by molecular models. A good resolution was

obtained by recording the spectrum at −27 °C, where the compound was essentially frozen in its most stable conformation (see the Supporting Information). It appeared therefore that kirkine and fortucine were either diastereoisomers or double-bond isomers. In order to distinguish between these two possibilities, we subjected our synthetic product and authentic kirkine to catalytic hydrogenation and obtained the same compound **15**, as confirmed by NMR spectroscopy, TLC, and HRMS (the only difference is that our sample is racemic). Therefore, kirkine has structure **14** in which the olefin has the same position as in siculinine (**3**).[5c] It is the only isomer that is compatible with the NMR spectra and that would lead to **15** upon catalytic reduction.

In summary, we have devised a concise (12 steps, 9% overall yield) first total synthesis of (±)-fortucine (**2**) and corrected the structure of kirkine, which should be revised to **14**. The synthetic route is noteworthy for its stereo- and regioselective radical cascade process as well as the multifaceted use of hydrazone **8**.

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[1] D. R. Dalton, *The Alkaloids: The Fundamental Chemistry—A Biogenetic Approach*, Marcel Dekker, New-York, **1979**.
[2] J. L. Hartwell, *Lloydia* **1967**, *30*, 379.
[3] a) S. F. Martin in *The Alkaloids*, *Vol. 30* (Ed.: A. Brossi), Academic Press, New York, **1987**, pp. 251–376; b) S. Ghosal, K. S. Saini, S. Razdan, *Phytochemistry* **1985**, *24*, 2141; c) T. Mineshita, K. Yayaguchi, K. Takeda, K. Kotera, *Annu. Rep. Shionogi Res. Lab.* **1956**, *6*, 119; d) U. Chattopadhyay, L. Chaudhuri, S. Das, Y. Kumar, S. Ghosal, *Pharmazie* **1984**, *39*, 855; e) P. Leo De, G. Dalessandro, A. De Santis, O. Arigoni, *Plant Cell Physiol.* **1973**, *14*, 487.
[4] a) S. Takagi, W. I. Taylor, S. Uyeo, H. J. Yajima, *J. Chem. Soc.* **1955**, 4003; b) H. Fales, E. M. Warnhoff, W. C. Wildman, *J. Am. Chem. Soc.* **1955**, *77*, 5885.
[5] a) G. M. Tokhtabaeva, V. I. Sheichenko, I. V. Yartseva, O. N. Tolkachev, *N. Khim. Prir. Soedin.* **1987**, 727; b) J. Bastida, C. Codina, P. Peeters, M. Rubiralta, M. Orozco, F. J. Luque, S. C. Chharbra, *Phytochemistry* **1995**, *40*, 1291; c) P. Richomme, V. Pabuccuoglu, T. Gozler, A. J. Freyer, M. Shamma, *J. Nat. Prod.* **1989**, *52*, 1150.
[6] a) J. M. Watt, M. G. Breyer-Brandwijk in *Medicinal and Poisonous Plants of Souther and Eastern Africa*, E. & S. Livingstone Ltd., Edinburgh, **1962**; b) J. O. Kokwaro in *Medicinal Plants of East Africa*, East Africa Literature Bureau, Kampala, **1976**.
[7] M. E. Trân-Huu-Dâu, R. Wartchow, E. Winterfeldt, Y. S. Wong, *Chem. Eur. J.* **2001**, *7*, 2349.
[8] Formed by the condensation of acetaldehyde with 1-(methylthio)thiocarbonyl-1-phenyl-hydrazine, see Ref. [9a].
[9] a) A. C. Callier-Dublanchet, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1995**, *36*, 8791; b) A. C. Callier-Dublanchet, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1997**, *38*, 2463; c) M. Depature, J. Grimaldi, J. Hatem, *Eur. J. Org. Chem.* **2001**, 941.
[10] a) X. Hoang-Cong, B. Quiclet-Sire, S. Z. Zard, *Tetrahedron Lett.* **1999**, *40*, 2125; b) G. L. Barclay, B. Quiclet-Sire, G. Sanchez-Jimenez, *Org. Biomol. Chem.* **2005**, *3*, 823.

