ORGANIC LETTERS

2000
Vol. 2, No. 17
2639−2641

A New Route to Spirooxindoles

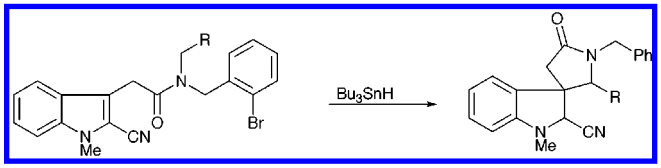
Stephen T. Hilton, Tim C. T. Ho, Goran Pljevaljcic, and Keith Jones*

School of Chemical and Pharmaceutical Sciences, Kingston University, Penrhyn Road, Kingston-upon-Thames, Surrey, KT1 2EE, U.K.

keith.jones@kingston.ac.uk

Received June 6, 2000

ABSTRACT



Reaction of indole amides 5 with tributylstannane gave spiroindolenines 9 which are readily converted into spiropyrrolidinyloxindoles. This tricyclic system is found in a number of interesting natural products.

A growing number of alkaloids containing the spiropyrrolidinyloxindole skeleton are being discovered. These represent a wide range of structural complexity, from the simpler members of the class such as horsfiline **1**[1] and elacomine **2**[2] to the more complex members such as alstonisine **3**[3] in which the pyrrolidine portion is part of a bicyclic system (Figure 1). Recently, spirotryprostatin A **4** has been isolated from

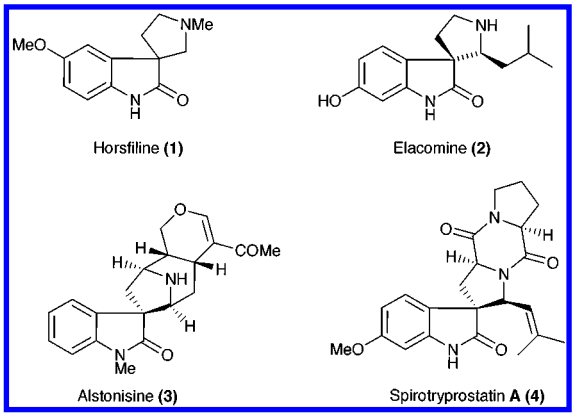


Figure 1. Spirooxindole natural products.

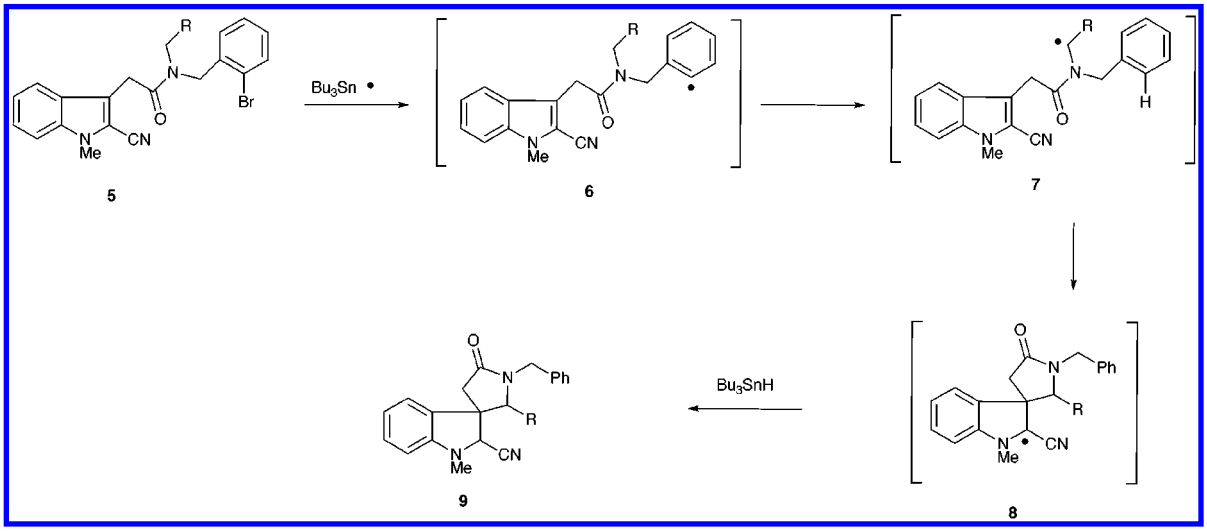
the fermentation broth of *Aspergillus fumigatus* and shown to inhibit the cell cycle and hence have potential as an antineoplastic agent.[4] There have been a number of total syntheses of horsfiline published[5] as well as a thorough synthetic study on elacomine and its diastereomer,[6] limited work on alstonisine,[7] and a recent synthesis of spirotryprostatin A.[8] The elacomine synthesis and the approaches to alstonisine and spirotryprostatin all proceed through a tetrahydrocarboline to oxindole rearrangement. Some years ago, we published the first total synthesis of horsfiline **1** using an aryl radical cyclization.[5a] In trying to extend our chemistry to the more complex elacomine **2**, we encountered problems with the regiochemistry of the radical cyclization[9] which led us to completely alter our approach to these compounds. It is this new route that we wish to describe in this Letter.

The new route is based on the novel tandem radical sequence shown in detail in Scheme 1. Reaction of indole amide **5** with the tributylstannyl radical will produce the aryl radical **6** by bromine atom abstraction. In the absence of

(1) Jossang, A.; Jossang, P.; Hadi, H. A.; Sévenet, T.; Bodo, B. *J. Org. Chem.* **1991**, *56*, 6527.
(2) James, M. N. G.; Williams, G. J. B. *Can. J. Chem.* **1972**, *50*, 2407.
(3) Elderfield, R. C.; Gilman, R. E. *Phytochemistry* **1972**, *11*, 339.
(4) Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527.
(5) (a) Jones, K.; Wilkinson, J. *J. Chem. Soc., Chem. Commun.* **1992**, 1767. (b) Bascop, S. I.; Sapi, J.; Laronze, J. Y.; Levy, J. *Heterocycles* **1994**, *38*, 725. (c) Pellegrini, C.; Strassler, C.; Weber, M.; Borschberg, H. J. *Tetrahedron: Asymmetry* **1994**, *5*, 1979. (d) Palmisano, G.; Annunziata, R.; Papeo, G.; Sisti, M. *Tetrahedron: Asymmetry* **1996**, *7*, 1. (e) Lakshmaiah, G.; Kawabata, T.; Shang, M. H.; Fuji, K. *J. Org. Chem.* **1999**, *64*, 1699.
(6) Pellegrini, C.; Weber, M.; Borschberg, H. J. *Helv. Chim. Acta* **1996**, *79*, 151.
(7) Peterson, A. C.; Cook, J. M. *J. Org. Chem.* **1995**, *60*, 120. Yu, P.; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 8799.
(8) Edmonson, S.; Danishefsky, S. J.; Sepp-Lorenzino, L.; Rosen, N. *J. Am. Chem. Soc.* **1999**, *121*, 2147.
(9) Ho, T. C. T. Ph.D. Dissertation, University of London, London, U.K., 1997.

10.1021/ol0061642 CCC: $19.00
Published on Web 08/02/2000

Scheme 1



energetically preferred reactions, aryl radicals are well known to undergo [1,5]-hydrogen atom abstraction[10] which in this case should generate the α-amido radical **7**. A report by Fang[11] has shown that alkyl radicals will add intramolecularly to the 3-position of 2-cyanoindoles which in our case will generate spiropyrrolidinyl indolenine radical **8**. Reduction of this stabilized radical with tributyltin hydride (TBTH) will generate cyanoindolenine **9** and more tributylstannyl radical. Transformation of the cyanoindolenine to the oxindole by oxidative decyanation is well precedented.[12]

The synthesis of cyclization precursors **5** commenced with indole-3-acetic acid **10** (Scheme 2). Formation of the methyl ester using thionyl chloride in methanol at −78 °C followed by *N*-methylation using sodium hydride and methyl iodide gave the *N*-methylindole **11** in 91% overall yield. Vilsmeier formylation of **11** proceeded in some 67% yield on a small scale, but on a larger scale the yield of 2-formylindole **12** was consistently around 50%. Formation of the oxime **13** using hydroxylamine hydrochloride in ethanol containing pyridine was uneventful, and elimination in refluxing acetic anhydride using triethylamine gave the 2-cyanoindole **14** in 69% yield from the aldehyde **12**. Hydrolysis of the ester to enable elaboration to the required amide proved to be rather troublesome. Most of the base-promoted conditions explored led to concomitant hydrolysis of the nitrile to the primary amide possibly via a mechanism involving intramolecular catalysis by the ester group. However, the very mild conditions reported by Boger[13] involving lithium hydroxide in a *tert*-butyl alcohol/water mixture at room temperature proved successful and gave the acid **15** in 97% yield. Coupling of the acid **15** with amines using DCC proved to be rather low yielding, and so **15** was converted to the acid chloride **16** by careful reaction with oxalyl chloride in THF at 0 °C. Reaction with 2-bromobenzylamine as its hydrochloride salt using an excess of diisopropylethylamine in dichloromethane gave the primary amide **17** in 94% yield. Unfortunately, it proved impossible to alkylate **17** on the amide nitrogen using base and alkyl halide owing to what appears to be a cyclization onto the nitrile. Consequently, acid chloride **16** was reacted with *N*-methyl-2-bromobenzylamine and *N*-ethyl-2-bromobenzylamine[14] to give the desired radical precursors **5a** and **5b**, respectively, in 84% and 90% yields.

With these two substrates in hand, we were in a position to study the radical sequence. However, NMR studies of **5a** and **5b** clearly demonstrated that two amide rotamers were present in each case in approximately equal amounts. It is well established that the lifetime of radicals is generally insufficient to allow amide bond rotation to occur.[15] In the case of **5**, one of the two rotamers would be unable to cyclize onto the indole-3-position owing to its geometry and would undergo reduction leading to a maximum yield for the sequence of 50%. To aid rotamer interconversion, we carried out the radical reactions in high-boiling solvents, although the results indicate this has little beneficial effect. Reaction of **5a** in *tert*-butylbenzene at 170 °C with TBTH using AIBN as initiator and syringe pump delivery gave a 30% yield of the spirocyclic indolenine **9a** as a 1:1 mixture of diastereomers. The proton NMR of the individual diastereomers of **9a** showed three AB quartets for the three methylene groups and a singlet for the proton adjacent to the nitrile. Along with the desired product, some 60% of reduced product was isolated, mainly arising from the "wrong" amide rotamer, and a small amount of starting material was recovered,

(10) Curran, D. P.; Xu, J. Y. *J. Am. Chem. Soc.* **1996**, *118*, 3142. Beckwith, A. L. J.; Storey, J. M. D. *J. Chem. Soc., Chem. Commun*. **1995**, 977.

(11) Yang, C. C.; Chang, H. T.; Fang, J. *J. Org. Chem.* **1993**, *58*, 3100.

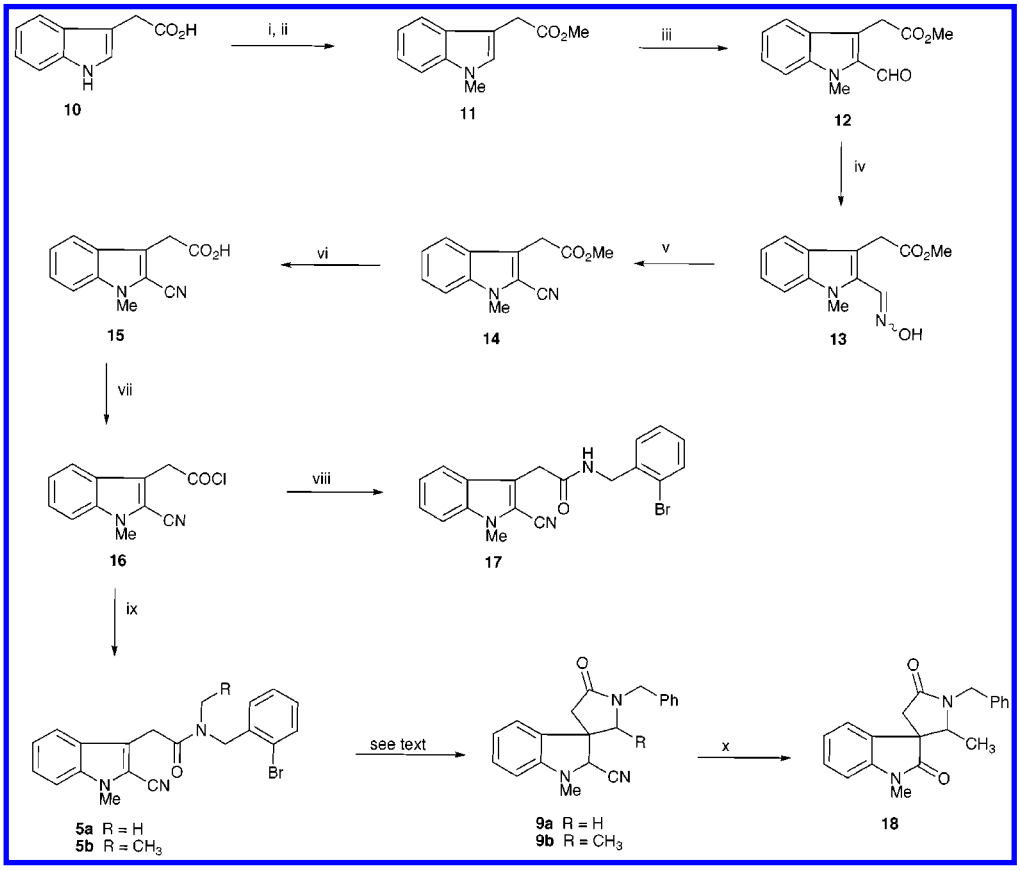
(12) Fang, J. M.; Chuang, T. H.; Yang, C. C.; Chang, C. J. *Synlett* **1990**, 733

(13) Boger, D. L.; Borzilleri, R. M.; Nukui, S.; Beresis, R. T. *J. Org. Chem.* **1997**, *62*, 4721.

(14) These secondary amines were prepared by the procedure reported by Fukuyama: Fukuyama, T.; Jow, C.-K.; Cheung, M. *Tetrahedron Lett.* **1995**, *36*, 6373. See also: Bowman, W. R.; Coghlan, D. R. *Tetrahedron* **1997**, *53*, 15787.

(15) Jones, K.; McCarthy, C. *Tetrahedron Lett.* **1989**, *30*, 2657. Musa, O. M.; Horner, J. H.; Newcomb, M. *J. Org. Chem.* **1999**, *64*, 1022.

Scheme 2[a]



[a] Reagents and conditions: i, $SOCl_2$, MeOH, −78 to 25 °C, 12 h, 99%; ii, NaH, THF, CH_3I, 0 °C, 92%; iii, DMF, $POCl_3$, 40 °C, 50%; iv, $NH_2OH.HCl$, EtOH, pyrdine, reflux, 4 h, 95%; v, Ac_2O, NEt_3, reflux, 4 h, 72%; vi, $LiOH·H_2O$, t-BuOH:H_2O (2:1), 25 °C, 24 h, 97%; vii, $(COCl)_2$, THF, 0 °C; viii, 2-bromobenzylamine hydrochloride, diisopropylethylamine, CH_2Cl_2, 0 °C, 94% from **15**; ix, as viii using *N*-methyl-2-bromobenzylamine for **5a**, 84% and *N*-ethyl-2-bromobenzylamine for **5b**, 90%; x, KOtBu, O_2, THF, 20 °C, 1 h, 41%.

indicating a poor radical chain. The recovered starting material and the reduced product were both equal mixtures of amide rotamers, indicating that equilibration occurs under these conditions but at too slow a rate to have an effect on the radical chemistry. A very similar yield was obtained by carrying out the reaction in refluxing *tert*-butyl-*m*-xylene (206 °C), but no starting material remained. Attempts to give the intermediate radicals a longer lifetime before reduction by using tristrimethylsilylsilane[16] gave a complex mixture with evidence of addition to the solvent. The success of this cyclization, in which a primary alkyl radical is generated by a [1,5]-hydrogen atom abstraction, gave us considerable cause for optimizm for the reaction of **5b** which involves a secondary alkyl radical.[17] Reaction in *tert*-butylbenzene under the same conditions as for **5a** gave a 53% yield of **9b** as a mixture of four diastereomers consisting of two major and two minor isomers. Again the proton NMR was distinctive, showing two AB quartets and a doublet for the methyl group in each diastereomer. Finally, the mixture of diastereomers of **9b** was converted in moderate yield to oxindole **18** (as a 1:1.3 ratio of two diastereomers) on treatment with potassium *tert*-butoxide and oxygen in THF.[12]

In summary, we have developed a novel route to spiropyrrolidinyloxindoles which utilizes a tandem radical sequence involving a [1,5]-hydrogen atom abstraction/cyclization. The synthesis is highly convergent and flexible. We are now investigating the application of this chemistry to the preparation of natural products and their analogues.

Acknowledgment. We thank Kingston University and EU for funding this research. We are also grateful to Dr. J. M. D. Storey for helpful discussions.

OL0061642

(16) Chatgilialoglu, C.; Griller, D.; Lesage, M. *J. Org. Chem.* **1988**, *53*, 3641.

(17) Curran, D. P.; Shen, W. *J. Am. Chem. Soc.* **1993**, *115*, 6051.