Pergamon

Tetrahedron Letters, Vol. 38, No. 24, pp. 4327-4328, 1997

0040-4039/97 $17.00 + 0.00

PII: S0040-4039(97)00892-7

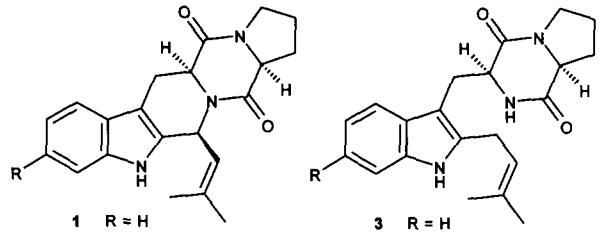
Concise Synthesis of the Cell Cycle Inhibitor Demethoxyfumitremorgin C

Haishan Wang and Arasu Ganesan*

Institute of Molecular and Cell Biology, National University of Singapore, 10 Kent Ridge Crescent, Singapore 119260

Abstract: Reaction of the imine derived from L-tryptophan methyl ester and senecialdehyde with Fmoc-L-Pro-Cl induces an acyliminium Pictet-Spengler condensation, yielding a mixture of cis and trans tetrahydro-β-carbolines. Deprotection of the cis product with concomitant diketopiperazine formation afforded the natural product in 20 % overall yield.

Recently, Osada *et al.* developed[1] a bioassay for the discovery of mammalian cell cycle inhibitors. Using this method, they identified[2] a series of diketopiperazines from the fermentation broth of *Aspergillus fumigatus* BM939. These alkaloids include demethoxyfumitremorgin C (**1**) and the previously known fumitremorgin C (**2**), together with their plausible biogenetic precursors tryprostatin B (**3**) and tryprostatin A (**4**). Syntheses of the tryprostatins have since appeared.[3] We focused our attention on **1**, the most biologically active member of this series (IC_{50} values for **1-4** are 0.45, 4.1, 4.4, and 16.4 μM respectively), and here wish to report a concise synthesis.



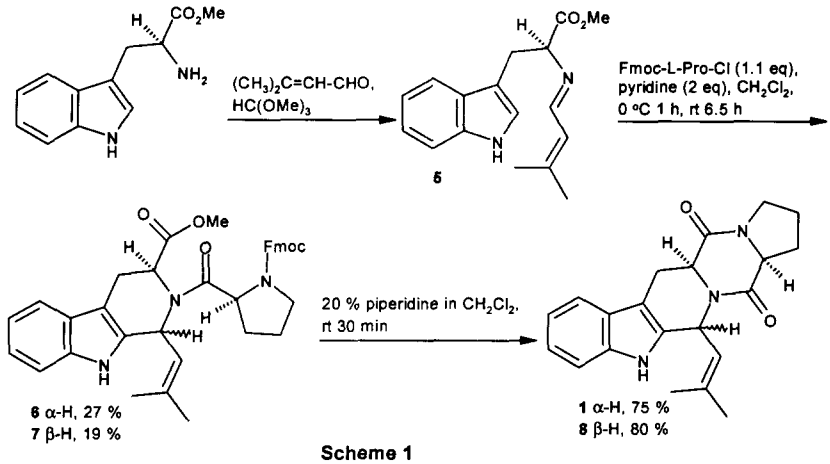
1 R = H
2 R = OMe

3 R = H
4 R = OMe

Prior to its isolation as a natural product, **1** was prepared[4] by O'Malley and Cava in 1987, as a model for the tremorgenic mycotoxin[5] fumitremorgin C (**2**). They employed a chloroformate induced Pictet-Spengler condensation[6] to give a 2:1 mixture of tetrahydro-β-carbolines. The minor isomer was carried forward to **1** in a total of six steps. Later, the groups of Nakagawa and Hino[7] as well as Bailey[8] also synthesized **1**. These routes used a masked senecialdehyde in the Pictet-Spengler reaction, resulting in higher yields. However, subsequent generation of the prenyl side chain resulted in alkene mixtures.

In our synthesis (Scheme 1), we have succeeded in using the direct combination of senecialdehyde and proline in the Pictet-Spengler reaction, enabling rapid assembly of the natural product. Reaction of L-tryptophan methyl ester and senecialdehyde in trimethyl orthoformate[9] generated imine **5**. The crude imine was treated with Fmoc-L-Pro-Cl[10] to afford a 1.4:1 mixture of the cis tetrahydro-β-carboline **6** and the trans diastereomer **7**. Interestingly, in a recent study[11] with tryptamine, Pictet-Spengler products were not observed with α,β-unsaturated imines. The ratio of products in our cyclization is also noteworthy. In an earlier example[12] with isovaleraldehyde and L-Cbz-Pro-Cl, the trans epimer predominated. The difference may be due to our use of the more bulky Fmoc group.[13]

The tetrahydro-β-carbolines **6** and **7** were readily separated[14] by chromatography and subjected to removal of the Fmoc group with simultaneous diketopiperazine cyclization,[15] yielding the natural product **1** and its epimer **8** respectively. Synthetic demethoxyfumitremorgin C was identical (TLC, mp, ^1H and ^{13}C NMR) to an authentic sample, and had an optical rotation of $[\alpha]^{22}_D$ = +16.4° (c 0.14, $CHCl_3$), lit: natural[2c] $[\alpha]^{30}_D$ = +8.0° (c 0.2, $CHCl_3$), synthetic[8] $[\alpha]^{24}_D$ = +19.1° (c 0.11, $CHCl_3$). We are presently optimising the conditions of our acyliminium cyclization and applying it to the synthesis of analogues for biological evaluation.



Scheme 1

Acknowledgement: We are grateful to Professor Hiroyuki Osada for providing a sample of demethoxyfumitremorgin C. This work was supported by grants from the National Science and Technology Board of Singapore.

References and Notes

1. Osada, H.; Cui, C.-B.; Onose, R.; Hanaoka, F. *Bioorg. Med. Chem.* **1997**, *5*, 193-203.
2. (a) Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Ubukata, M.; Takahashi, I.; Isono, K.; Osada, H. *J. Antibiot.* **1995**, *48*, 1382-1384. (b) Cui, C.-B.; Kakeya, H.; Okada, G.; Onose, R.; Osada, H. *J. Antibiot.* **1996**, *49*, 527-533. (c) Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 534-540. (d) Cui, C.-B.; Kakeya, H.; Osada, H. *J. Antibiot.* **1996**, *49*, 832-835. (e) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1996**, *52*, 12651-12666. (f) Cui, C.-B.; Kakeya, H.; Osada, H. *Tetrahedron* **1997**, *53*, 59-72.
3. (a) Tryprostatin A: Gan, T.; Cook, J. M. *Tetrahedron Lett.* **1997**, *38*, 1301-1304. (b) Tryprostatin B: Depew, K. M.; Danishefsky, S. J.; Rosen, N.; Sepp-Lorenzino, L. *J. Am. Chem. Soc.* **1996**, *118*, 12463-12464.
4. O'Malley, G.; Cava, M. P. *Tetrahedron Lett.* **1987**, *28*, 1131-1134.
5. For a review see: Steyn, P. S.; Vleggaar, R. In *Fortschritte der Chemie organischer Naturstoffe,* Vol. 48; Herz, W.; Grisebach, H.; Kirby, G. W.; Tamm, Ch., Eds.; Springer Verlag: Wien, 1985; pp 1-80.
6. For an excellent review, see: Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797-1842.
7. Kodato, S.-I.; Nakagawa, M.; Hongu, M.; Kawate, T.; Hino, T. *Tetrahedron* **1988**, *44*, 359-377.
8. Bailey, P. D.; Hollinshead, S. P.; McLay, N. R.; Everett, J. H.; Reynolds, C. D.; Wood, S. D.; Giordano, F. *J. Chem. Soc. Perkin Trans. I* **1993**, 451-458.
9. Look, G. C.; Murphy, M. M.; Campbell, D. A.; Gallop, M. A. *Tetrahedron Lett.* **1995**, *36*, 2937-2940.
10. Carpino, L. A.; Cohen, B. J.; Stephens, K. E., Jr.; Sadat-Aalaee, S. Y.; Tien, J.-H.; Langridge, D. C. *J. Org. Chem.* **1986**, *51*, 3732-3734.
11. Schmidt, G.; Waldmann, H.; Henke, H.; Burkard, M. *Chem. Eur. J.* **1996**, *2*, 1566-1571.
12. Nakagawa, M.; Fukushima, H.; Kawate, T.; Hongu, M.; Kodato, S.-I.; Une, T.; Taniguchi, M.; Hino, T. *Tetrahedron Lett.* **1986**, *27*, 3235-3238.
13. In the Cava synthesis (ref 4), the cis product was formed only with a sterically hindered chloroformate.
14. The separation is best carried out at this stage prior to diketopiperazine formation.
15. Beyermann, M.; Bienart, M.; Niedrich, H.; Carpino, L. A.; Sadat-Aalaee, D. *J. Org. Chem.* **1990**, *55*, 721-728.

(*Received in UK* 24 *April* 1997; *accepted* 2 *May* 1997)