Pergamon

Tetrahedron Letters, Vol. 35, No. 32, pp. 5769-5770, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01175-3

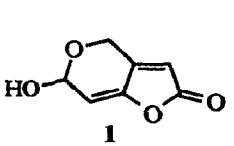
An Efficient Total Synthesis of Neopatulin

John Boukouvalas* and François Maltais

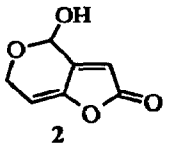
Département de Chimie, Université Laval, Québec (Québec), Canada G1K 7P4

Abstract: A new, highly efficient synthesis of neopatulin (**1**) has been achieved through Lewis acid-catalysed aldol reaction of 2-formyl-1,3-dithiane (**4**) with 2-(*tert*-butyldimethylsiloxy)-4-[(*tert*-butyldimethylsiloxy)-methyl]furan (**5**).

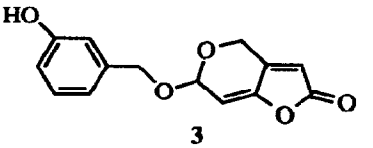
Neopatulin (**1**)[1] is a redox isomer and pivotal biogenetic precursor[2] of the potent antibiotic patulin (**2**) which is produced by numerous fungal species, notably of the genera *Penicillium* and *Aspergillus*.[3] Whereas neopatulin has not yet been evaluated pharmacologically, its O-*m*-hydroxybenzyl derivative, coined "anticancer 4148A" (**3**), exhibits strong cytotoxic activity against human cell lines of leukemia and mouth cancer (IC_{50} = 0.25-0.8 μg/mL).[4] At a glance, these molecules look deceptively simple. A closer inspection, however, reveals that they display a variety of densely packed, sensitive functionality. These features have made patulin a notoriously elusive synthetic target since the pioneering work of Woodward and Singh nearly half a century ago.[5] In recent years, patulin was prepared from L-arabinose by two virtually identical routes involving sequential destruction of all three chiral centres present in the starting material.[6,7] Likewise, the first and only documented synthesis of neopatulin was achieved by Pattenden *et. al.* in seven steps from D-lyxose.[6b]



1



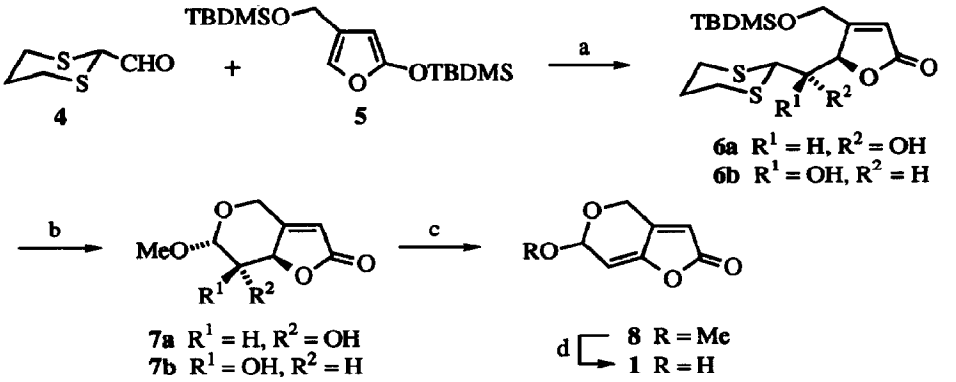
2



3

Herein we describe a new, highly efficient synthesis of **1** from two readily available achiral reagents, namely 2-formyl-1,3-dithiane (**4**)[8] and 2-(*tert*-butyldimethylsiloxy)-4-[(*tert*-butyldimethylsiloxy)-methyl]furan (**5**)[9] (Scheme). Aldol reaction of **4** with **5** in the presence of boron trifluoride etherate furnished the diastereomeric alcohols **6a** and **6b** (ratio 13:1) in 91% yield.[10] In accord with our previous findings on 2-trimethylsilyloxyfuran,[11] aldolisation of **5** occurred exclusively at the C(5) position with high *syn*-selectivity. Nonetheless, both diastereoisomers were equally useful for our purposes and their separation was not attempted. The deprotection of the masked aldehyde and alcohol groups of **6** proved to be a more difficult task than anticipated.[12] Of the several methods examined, the most expedient consisted of dethioacetalisation with mercury(II) perchlorate trihydrate (2.2 equiv.) in methanol[13] at 25 °C for 11 h followed by treatment with HCl (25 °C, 4 h) to remove the silyl group. This one-pot procedure provided pyranofuranone **7a**, contaminated with about 5% of its diastereoisomer **7b**, in a yield of 82% after purification by silica gel chromatography. Formal dehydration of this material to O-methyl neopatulin (**8**) was accomplished in 81% yield by mesylation (MsCl, DMAP, Et_3N) and subsequent treatment with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[14] Finally, hydrolysis of **8** with aqueous trifluoroacetic acid[6b] delivered neopatulin (**1**; 78%) whose melting point (88-90 °C) and spectroscopic properties (IR, ^1H and ^{13}C NMR) were in full agreement with those of the natural substance.[1]

Scheme



a) $BF_3{\cdot}Et_2O$, CH_2Cl_2, -78 °C (91%). b) $Hg(ClO_4)_2{\cdot}3H_2O$, MeOH, 25 °C; aq. 6N HCl (82%). c) MsCl, Et_3N, DMAP, CH_2Cl_2, 0 °C; DBU, 0 °C (81%). d) CF_3CO_2H, H_2O, 50 °C (78%).

The present synthesis of **1** is short, easy to perform and illustrates a novel strategy for pyranolactone construction. Efforts to extend this approach to the preparation of patulin and other naturally occurring ylidenebutenolides are currently underway in this laboratory.

Acknowledgement. We thank Laval University and the Natural Sciences and Engineering Research Council of Canada (NSERC) for financial support.

References and Notes

1. Sekiguchi, J.; Gaucher, G.M.; Yamada, Y. *Tetrahedron Lett.* **1979**, 41-42.
2. Sekiguchi, J.; Shimamoto, T.; Yamada, Y.; Gaucher, G.M. *Appl. Environ. Microbiol.* **1983**, *45*, 1939-1942. Priest, J.W.; Light, R.J. *Biochemistry* **1989**, *28*, 9192-9200.
3. Engel, G. and Teuber, M. In *Mycotoxins-Production, Isolation, Separation and Purification*, Betina, V., Ed.; Elsevier: Amsterdam, 1984, pp 291-314. Dulaney, E.L.; Jacobsen, C.A. *J. Antibiotics* **1987**, *40*, 1211-1212. Seigle-Murandi, F.; Steiman, R.; Krivobok, S.; Beriel, H.; Benoit-Guyod, J.-L. *Pharmazie* **1992**, *47*, 288-291.
4. Mizogami, K.; Mikami, A.; Okazaki, T.; Hanada, K. Jpn. Kokai Tokkyo Koho JP 03,169,881 [91,169,881] , July 23, 1991 (*CA:* **1992**, *116*, 82219d).
5. Woodward, R.B.; Singh, G. *J. Am. Chem. Soc.* **1950**, *72*, 1428, 5351-5352 and cited references.
6. (a) Gill, G.B.; Pattenden, G.; Stapleton, A. *Tetrahedron Lett.* **1988**, *29*, 2875-2878. (b) Bennett, M.; Gill, G.B.; Pattenden, G.; Shuker, A.J.; Stapleton, A. *J. Chem. Soc., Perkin Trans. 1* **1991**, 929-937.
7. Seijas, J.A.; Tato, M.P.V.; Estévez, R.; Castedo, L. Riguera, R. *Heterocycles* **1989**, *29*, 181-184.
8. Meyers, A.I.; Strickland, R.C. *J. Org. Chem.* **1972**, *37*, 2579-2583.
9. Prepared in 4 steps (45% overall yield) from dihydroxyacetone dimer: Sledeski, A.W. *Alkylation Régiosélective de Trialkylsilyloxy-2 Furannes. Application à la Synthèse de γ-Lactones, et de Furannes d'Origine Naturelle*, University of Geneva 1990. See also: Jefford, C.W.; Rossier, J.-C.; Boukouvalas, J.; Huang, P. *Helv. Chim. Acta* **1994**, *77*, 661-667.
10. Yields refer to chromatographically isolated, fully characterized products.
11. Jefford, C.W.; Jaggi, D.; Boukouvalas, J. *Tetrahedron Lett.* **1987**, *28*, 4037-4040. Jefford, C.W.; Jaggi, D.; Sledeski, A.W.; Boukouvalas, J. In *Studies of Natural Products Chemistry*, Stereoselective Synthesis (Part B); Atta-ur-Rahman, Ed.; Elsevier: Amsterdam, 1989; Vol. 3, pp. 157-171.
12. Although clean desilylation was effected by using HCl in MeOH (but not with *n*-Bu_4NF in THF), subsequent hydrolysis of the dithiane proved to be troublesome under a variety of conditions.
13. Fujita, E.; Nagao, Y.; Kaneko, K. *Chem. Pharm. Bull.* **1978**, *26*, 3743-3751. Konradi, A.W.; Pedersen, S.F. *J. Org. Chem.* **1990**, *55*, 4506-4508. The courtesy extended by Prof. Steven Pedersen in providing an experimental procedure is deeply appreciated.
14. The need for a stronger base (DBU) arose from the reluctance of **7a**, unlike **7b** (*cf.* ref. 6b), to undergo spontaneous elimination under the mesylation conditions.

(*Received in USA* 2 *June* 1994; *accepted* 15 *June* 1994)