Pergamon

Tetrahedron Letters, Vol. 35, No. 44, pp. 8101-8102, 1994
Elsevier Science Ltd
Printed in Great Britain
0040-4039/94 $7.00+0.00

0040-4039(94)01762-X

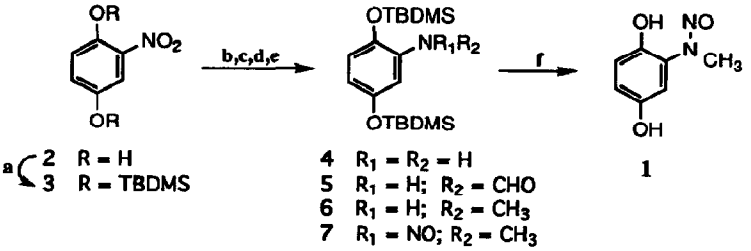
Synthesis of Dephostatin, a Novel Protein Tyrosine Phosphatase Inhibitor

Pierre Hamel* and Yves Girard

Merck Frosst Centre for Therapeutic Research, P.O. Box 1005, Pointe-Claire - Dorval, Québec H9R 4P8

Abstract: The novel protein tyrosine phosphatase inhibitor dephostatin was synthesized in 6 steps with an overall yield of 35% from 2-nitrohydroquinone

In recent publications, Umezawa et al.[1,2] have described the isolation and characterization of a novel protein tyrosine phosphatase inhibitor produced by *Streptomyces*. They named this material dephostatin, and determined that its chemical structure is 2-(N-Methyl-N-nitroso) hydroquinone **1** based on its physico-chemical properties and also on its transformation to two derivatives that were also adequately characterized. In view of the tedious manipulations necessary for the isolation of dephostatin from cell cultures, we felt that, due to the relatively simple nature of the molecule, a synthetic approach would make dephostatin more readily available to interested investigators. We present herein a convenient synthesis of dephostatin, in 6 steps from a readily available starting material, 2-nitrohydroquinone (**2**).



Reagents: **a**: t-BuMe$_2$SiCl, imidazole, DMF, r.t. (quant). **b**: NaBH$_4$, NiCl$_2$.6H$_2$O, MeOH, r.t. (83%). **c**: acetic-formic anhydride, HCOOH, 0°C (92%). **d**: BH$_3$, THF, r.t. (95%). **e**: NOBF$_4$, Et$_3$N, ether (78%). **f**: TBAF, THF, 0°C (62%).

The starting material 2-nitrohydroquinone **2** was obtained by oxidation of *o*-nitrophenol using ammonium persulfate under basic aqueous conditions, as described by Forrest and Petrow.[3] A blocking group for the two phenolic groups was necessary and its choice was directed by careful evaluation of the subsequent steps, including easy removal in the final step of the sequence. Protection as *tert*-butyldimethyl silyl ethers proved to be quite adequate for this task.

When the diprotected nitro compound **3** was initially subjected to catalytic hydrogenation in the presence of 5% palladium on charcoal at 40 psi in ethanol, a low yield of amine was obtained, along with side-products which suggested loss of protecting group and also transfer to the amine group. Alternatively, nitro reduction via the procedure of Kudo[4] using $NaBH_4$ and nickel (II) chloride in methanol at room temperature cleanly provided the amine **4**, in 83% yield. Formylation using acetic-formic anhydride in formic acid at 0° afforded the N-formyl derivative **5**, which was easily reduced to the corresponding methylamine **6** by borane-THF at room temperature. Conversion to the final precursor **7** was achieved cleanly by nitrosation using freshly sublimed nitrosonium tetrafluoroborate[5] in dry ether, in the presence of 1.5 eq of Et_3N at room temperature. Removal of the *tert*-butyldimethyl silyl protecting groups was achieved with 2.2 eq of TBAF in THF at 0° followed by quenching with aq NH_4Cl. The dephostatin was purified by column chromatography on silica gel, using 1:1 ethyl acetate/hexane as eluent; the product obtained was stirred with 1:1 ether/hexane at room temperature[6] for 1.5 hours and filtered to afford pure dephostatin as a tan solid, mp: dec 120° (lit[2], 104-107°C). Overall yield from 2-nitrohydroquinone is calculated at 35%.[7]

Characterization data for our synthetic dephostatin[8] allow us to confirm the identity of our material with that from culture isolation. Each step of the synthesis may be run on multi-gram scale, and all intermediates are stable compounds which gave satisfactory spectral and analytical data. The dephostatin revealed itself to be unstable on storage at room temperature; however, a sample kept at 0° showed only slight deterioration after 4 months. We thus recommend storage at -78°C in the absence of light.

REFERENCES AND NOTES

1. Imoto, M; Kakeya H.; Sawa T.; Hayashi, C; Hamada, M; Takeuchi, T; Umezawa, K. *J. Antibiotics* **1993**, *46*, 1342.
2. Kakeya, H ; Imoto, M.; Takahashi, Y; Naganawa, H; Takeuchi, T.; Umezawa, K. *J. Antibiotics*, **1993**, *46*, 1716.
3. Forrest, J; Petrow, V. *J. Chem Soc.* **1950**, 2340.
4. Nose, A , Kudo, T *Chem. Pharm. Bull.* **1981**, *29*, 1159
5. Olah, G., Noszkó, L , Kuhn, S., Szelke, M. *Chem Ber.* **1956**, *89*, 2374.
6. This procedure efficiently removes TBAF side-products which contaminate the chromatographed product.
7. After submission of our manuscript, we became aware of a recent synthesis of dephostatin by Umezawa et al. *J. Chem. Soc. Chem. Commun.*, **1994**, 437. Their synthetic pathway is quite different and involves an unstable intermediate.
8. IR (KBr) 3260 (br), 1465, 1415, 1265, 1230 cm^{-1}; ^1H NMR (400 MHz, acetone-d_6) δ 3.35 (CH_3), 6.85 (m, 2H) 6.94 (d, J= 8.5 Hz, 1H), 8.15 and 8.45 (2 OH) Anal calc'd for $C_7H_8N_2O_3$: C, 50.00; H, 4.80; N, 16.66. Found: C, 50.21; H, 4.91; N, 16.36 MS c.i. (CH_4) m/z 169 (M+1), 139

(*Received in USA* 20 *July* 1994; *revised* 30 *August* 1994; *accepted* 1 *September* 1994)