Pergamon

Tetrahedron Letters 40 (1999) 4023–4026

TETRAHEDRON LETTERS

A Simple and Concise Synthesis of LY231514 (MTA)

Edward C. Taylor* and Bin Liu

Department of Chemistry, Princeton University

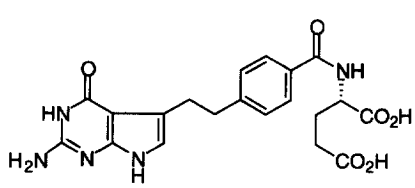
Princeton, New Jersey 08544

Received 12 March 1999; accepted 1 April 1999

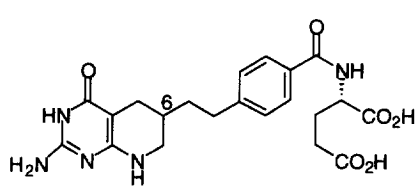
Abstract: The pyrrolo[2,3-d]pyrimidine anticancer agent LY231514 (MTA, **1**) has been prepared utilizing, as a key sequence, Michael condensation of 2,6-diamino-4(3H)-pyrimidinone (as the donor) with the nitro olefin **8**, followed by a Nef reaction that leads to the annulated pyrrole ring of **1**.

Keywords: antitumour compounds; nitrogen heterocycles; Michael reactions; cyclisation

Several years ago we synthesized N-[4-[2-(2-amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid (**1**, LY231514) as one of many analogues of methotrexate, aminopterin and folic acid prepared as potential inhibitors of folate-dependent enzymes that might be of use in cancer chemotherapy.[1] This compound turned out to be an extraordinarily effective chemotherapeutic agent broadly active against a wide range of solid tumors.[2] We first thought that its major focus of activity was against thymidylate synthase, which was unexpected since LY231514 had initially been designed as a potential inhibitor of glycinamide ribonucleotide formyltransferase, the same enzyme in the de novo purine biosynthesis pathway that is inhibited by DDATHF (**2**) and by lometrexol (**3**).[3] However, more recent investigations have shown that its remarkable activity appears to be associated with its ability to inhibit (following effective transport and intracellular polyglutamylation) *at least five major folate-dependent enzymes* - dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, thymidylate synthase, aminoimidazole ribonucleotide formyltransferase, and both domains of the C-1 tetrahydrofolate synthase enzyme.[4] LY231514 (now referred to as MTA, for multitargeted antifolate) is currently in Phase III clinical trials.



1 LY231514, MTA



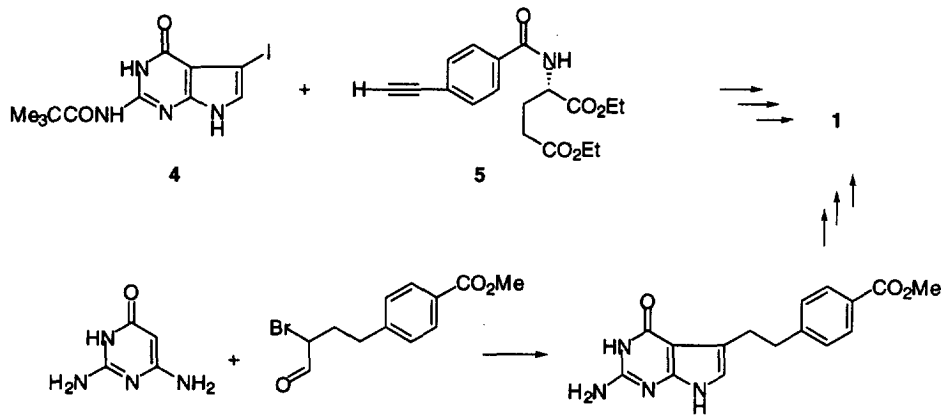
2 DDATHF (6R,S)
3 lometrexol ((6R)

Our original synthesis constructed the complete molecular framework of LY231514 through a palladium-catalyzed coupling of the 5-iodopyrrolopyrimidine **4** with diethyl 4 ethynylbenzoyl-L-glutamate **5**, followed by reduction of the triple bond, and final deprotection.[1] A different strategy by Barnett and coworkers utilized condensation of 2,6-diamino-4(3H)-pyrimidinone with an α-bromoaldehyde, followed by elaboration of the target glutamate derivative **1** (Scheme 1).[5] We describe in this Communication a concise and economical

0040-4039/99/$ - see front matter
PII: S0040-4039(99)00676-0

synthesis that couples the classical Nef reaction with the propensity of 2,6-diamino-4(3H)-pyrimidinone to undergo Michael additions at the unsubstituted C-5 position[6] (Scheme 2).

Scheme 1

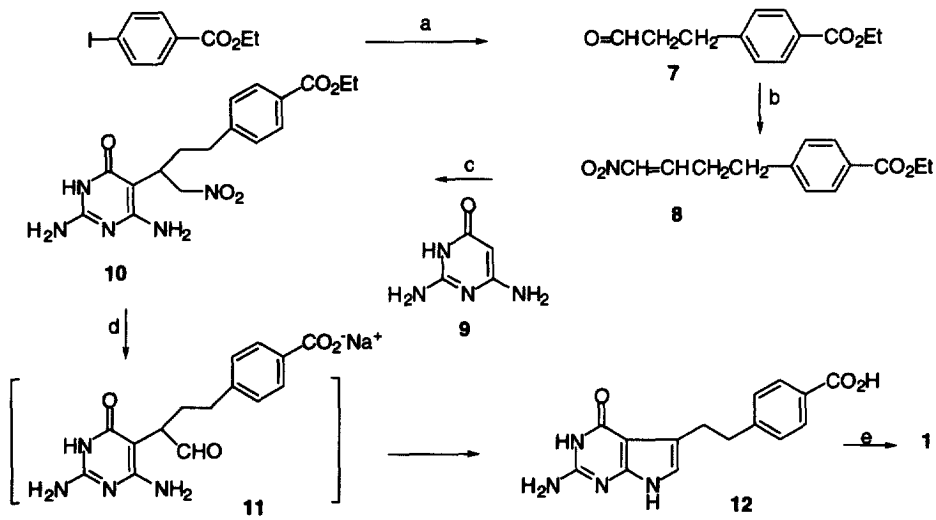


The requisite Michael acceptor, **8**, was prepared from methyl 4-iodobenzoate by palladium-catalyzed condensation with allyl alcohol to give 3-(4'-ethoxycarbonylphenyl)-1-propanal[7] (**7**, 98%), followed by aldol condensation with nitromethane and dehydration with methanesulfonyl chloride/triethylamine.[8] Condensation of this Michael acceptor with 2,6-diamino-4(3H)-pyrimidinone (**9**) was smoothly effected to give **10** in 91% yield simply by stirring at 50 °C for 24 hours in aqueous ethyl acetate. A one-pot, five-step conversion of **10** via the intermediate aldehyde **11** (not isolated) to 4-[2-(2-amino-4(3H)-oxo-7H-pyrrolo[2,3-d]pyrimidin-5-yl]ethylbenzoic acid (**12**, 57% overall yield from **10**) was then effected by stirring in dilute NaOH at room temperature for two hours, followed by addition to aqueous sulfuric acid at O °C. After three hours, the reaction mixture was worked up by basification with sodium hydroxide followed by acidification with acetic acid. Conversion of **12** to **1** involved conventional peptide coupling with diethyl L-glutamate/2-chloro-4,6-dimethoxy-1,3,5-triazine/N-methylmorpholine, and final saponification.

Pyrroles and fused pyrroles have been synthesized previously through Michael addition of β-carbonyl enamines with α-substituted nitroolefins[9] or α-substituted nitrosoolefins (prepared in situ from oximino ketones),[10] but we are unaware of a use of this concept to prepare α-unsubstituted pyrroles or fused pyrroles. This simple methodology should be capable of considerable further extension.[11]

ACKNOWLEDGEMENT: We are indebted to Eli Lilly & Co. for financial support of this work.

Scheme 2



[a] $Pd(OAc)_2$, allyl alcohol (98% yield); [b] (i) CH_3NO_2/NaOH/EtOH (72% yield); (ii) CH_3SO_2Cl/Et_3N (90% yield); [c] EtOAc/H_2O 1:1, 50 °C, 24 h (91% yield); [d] (i) aq. NaOH, rt, 2 h; (ii) add to aq. H_2SO_4 at O °C, 3 h; (iii) aq. NaOH to pH 7, rt,1 h; (iv) HOAc, then filter (overall yield 57%); [e] (i) diethyl L-glutamate.HCl, 4-methylmorpholine, 2-chloro-4,6-dimethoxy-1,3,5-triazine, rt (62% yield); (ii) NaOH THF/H_2O 1:1, rt (73% yield)

REFERENCES

1. Taylor, E. C.; Kuhnt, D.; Shih, C.; Rinzel, S. M.; Grindey, G. B.; Barredo, J.; Jannatipour, M.; Moran, R. G. *J. Med. Chem.* **1992**, *35*, 4450.

2. For example, see (a) Rinaldi, D. A.; Burris, H. A.; Dorr, F. A.; Woodworth, J. R.; Kuhn, J. G.; Eckardt, J. R.; Rodriguez, G.; Corso, S. W.; Fields, S. M.; Langley, C.; Clark, G.; Faries, D.; Lu, P.; Van Hoff, D. D. *J. Clin. Oncol.* **1995**, *13*, 2842. (b) Calvert, A. H.; Walling, J. M. *British J. Cancer* **1998**, *78* (Suppl), 35. (c) Hammond, L.; Baker, S. D.; Villalona-Calero, M.; Eckhardt, S. G.; Drengler, R.; Aylesworth, C.; Johnson, T.; Hidalgo, M.; Rodriguez, G.; Diab, S.; Monroe, P.; Thornton, D.; Johnson, R.; Von Hoff, D.; Rowinsky, E. *Ann. Oncol.* **1998**, *9* (Suppl), 160. (d) Johnson, T.; Schwartz, G.; McCune, D.; Stephenson, J.; Aylesworth, C.; Hammond, L.; Monroe, P.; Thornton, D.; Von Hoff, D.; Rowinsky, E. *Ann. Oncol.* **1998**, *9* (Suppl), 160. (e) John, W.; Clark, J.; Burris, H.; Picus, J.; Schulman, L.; Thornton, D.; Lochrer, P. *Proc. Am. Soc. Clin. Oncol.* **1997**, *16*, 292a-A1038. (f) Cripps, M. C.; Burnell, M.; Jolivet, J.; Lofters, W.; Fischer, B.; Panasci, L.; Iglesias, J.; Eisenhauer, E. *Eur. J. Cancer*, **1997**, *33* (Suppl. 8), S172-a768. (g) Rusthoven, J.; Eisenhauer, E.; Butts, C.; Gregg, R.; Dancey, J.; Fisher, B.; Iglesias, J. *Eur. J.*

Cancer **1997**, *33* (Suppl. 8), S231-a1045. (h) Thoedtmann, R.; Kemmerich, M.; Depenbrock, H.; Blatter, J.; Ohnmacht, U.; Rastetter, J.; Hanauske, A. R. *Eur. J. Cancer* **1997**, 33 (Suppl. 8), S247-a1116.

3. (a) For the original synthesis of DDATHF, see Taylor, E. C.; Harrington, P. J.; Fletcher, S. R.; Beardsley, G. P.; Moran, R. G. *J. Med. Chem.* **1985**, 28, 914. (b) Beardsley, G. P.; Moroson, B. A.; Taylor, E. C.; Moran, R. G. *J. Biol. Chem.* **1989**, 264, 328. (c) Moran, R.G.; Baldwin, S.W.; Taylor, E.C.; Shih, C. *J. Biol. Chem.* **1989**, 264, 21042. (d) Baldwin, S. W.; Tse, A.; Gossett, L. S.; Taylor, E. C., Rosowsky, A.; Shih, C.; Rinzel, S. M.; Grindey, G. B.; Barredo, J.; Jannatapour, M.; Moran, R. G. *J. Med. Chem.* **1992**, 35, 4450. (e) For reviews, see Taylor, E. C. *J. Heterocycl. Chem.* **1990**, 27, 1; Taylor, E. C. *Chemistry and Biology of Pteridines and Folates*, Ayling, J. E.; Nair, M. G.; Baugh, C. M., eds, Plenum Press, **1993**, pp. 387.

4. Shih, C.; Chen, V. J.; Gossett, L. S.; Gates, S. B.; MacKellar, W. C.; Habeck, L. L.; Shackelford, K. A.; Mendelsohn, L. G.; Soose, D. J.; Patel, V. F.; Andis, S. L.; Bewley, J. R.: Rayl, E. A.; Moroson, B. A.; Beardsley, G. P.; Kohler, W.; Ratnam, M.; Schultz, R. M. *Cancer Research* **1997**, *57*, 1116.

5. Barnett, C. J.; Wilson, T. M.; Kobierski, M. E. In *Chemistry and Biology of Pteridiines and Folates 1997* (Pfleiderer, W.; Rokos, H. eds), Blackwell Science, Berlin **1997**, p. 123.

6. (a) Taylor, E. C.; Dowling, J. E.; Schrader, T.; Bhatia, B. *Tetrahedron*, **1998**, *54*, 9507; (b) Anderson, G. L. *J. Heterocyclic Chem.* **1985**, *22*, 1469; (c) Bennett, G. B.; Mason, R. B. *J. Org. Chem.* **1977**, *42*, 1919; (d) Broom, A. D.; Shim, J. L.; Anderson, G. L. *J. Org. Chem.* **1976**, *41*, 1095; (e) Koen, M. J.; Gready, J. E. *J. Org. Chem.* **1993**, *58*, 1104; (f) Warner, J. C. In *The Chemistry of Heterocyclic Compounds*; Delia, T. J., Taylor, E. C., Eds.; Wiley: **1992**; Vol. 24, Part 4, p 20.

7. (a) Taylor, E. C.; Gillespie, P.; Patel, M. *J. Org. Chem.* **1992**, *57*, 3218. (b) Taylor, E. C.; Patel, H. H.; Jun, J.-G. *J. Org. Chem.* **1995**, *60*, 6684.

8. Melton, J.; McMurry, J. E. *J. Org. Chem.* **1975**, *40*, 2138.

9. (a) Grob, C. A.; Camenisch, K. *Helv. Chim. Acta* **1953**, *36*, 49. (b) Grob, C. A.; Schad, H. P. *Helv. Chim. Acta* **1955**, *38*, 1121; (c) Meyer, H. *Liebigs Ann. Chem.* **1981**, 1534; (d) Trautwein, A. W.; Jung, G. *Tetrahedron Lett.* **1998**, *39*, 8263.

10. Gibson, C. L.; Paulini, K.; Suckling, C. J. *Chem. Commun.* **1997**, 371.

11. For a related strategy for the synthesis of annulated furans, see (a) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1980**, *45*, 2945. (b) Miyashita, M.; Kumazawa, T.; Yoshikoshi, A. *J. Org. Chem.* **1984**, *49*, 3728.