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A novel synthetic route to 7-substituted derivatives of the antitumor agent LY231514 (MTA)

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Abstract

This paper describes a further synthesis of the pyrrolo[2,3-*d*]pyrimidine antitumor agent MTA (LY231514). Manganic triacetate dihydrate-induced radical cyclization of methyl *N*-crotyl-*N*-(3′,4′-dimethoxybenzyl)malonamide (**4d**) yielded the 3-carbomethoxy-2-pyrrolidinone **5d** that was then thiated with P_2S_5 to the corresponding thiolactam (**6d**). Cyclization with guanidine gave the 7-substituted 2-amino-4(3*H*)-oxo-5,6-dihydro-pyrrolo[2,3-*d*]pyrimidine (**7d**). Pd-catalyzed coupling with diethyl 4-iodobenzoylglutamate yielded (in a single step) the diethyl ester **9d**. Deprotection with H_2SO_4/TFA followed by saponification then gave MTA. Several additional 7-substituted derivatives of MTA were prepared by use of this methodology. In contradiction to a published claim, these 7-substituted derivatives proved to be devoid of any significant cell growth inhibitory activity.

Keywords: antitumor compounds; radical reactions; cyclization; coupling reactions.

N-{4-[2-(2-Amino-3,4-dihydro-4-oxo-7*H*-pyrrolo[2,3-*d*]pyrimidin-5-yl)ethyl]-benzoyl}-L-glutamic acid (LY231514, MTA, **1**) is proving to be an extraordinary antitumor agent.[1] This compound is a unique antifolate that inhibits (following intracellular polyglutamylation) at least five of the major folate-dependent enzymes (thymidylate synthase, dihydrofolate reductase, glycinamide ribonucleotide formyltransferase, aminoimidazole ribonucleotide formyltransferase and C-1 tetrahydrofolate synthetase).[2] Since our original synthesis of MTA in which the full molecular framework was obtained by means of an initial Pd-catalyzed coupling of 2-pivaloylamino-5-iodo-4(3*H*)-oxopyrrolo[2,3-*d*]pyrimidine with diethyl 4-ethynylbenzoyl-L-glutamate,[1a] two further syntheses have been published. In one, Barnett utilized an initial step involving condensation of 2,6-diamino-4(3*H*)-pyrimidinone with an α-bromoaldehyde;[3] in the other, we have described a concise synthesis involving Michael condensation of 2,6-diamino-4(3*H*)-pyrimidinone with an appropriate nitro olefin, followed by an intramolecular Nef reaction to form the annulated pyrrole ring.[4] The present paper describes a further new synthesis of MTA through deprotection of its 7-(3′,4′-dimethoxybenzyl) derivative, itself formed

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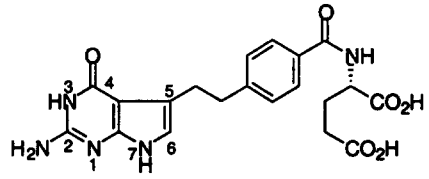
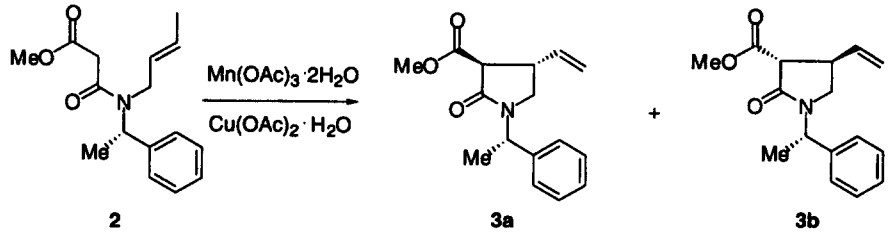
via an intermediate 4-ethenylpyrrolidinone obtained by radical cyclization of methyl *N*-crotyl-*N*-(3′,4′-dimethoxybenzyl)malonamide and a unique Pd-catalyzed coupling/double bond migration.



1 (LY231514, MTA)

A recent paper by Orena et al. describes a manganic triacetate dihydrate/cupric acetate hydrate-induced radical cyclization of methyl (*S*)-*N*-crotyl-*N*-(1-phenyleth-1-yl)malonamide (**2**) to yield a diastereomeric mixture of the 3-carbomethoxy-2-pyrrolidinones **3a,b** (Scheme 1).[5] We prepared the pyrrolidinone **5a** in 97% yield as described by Orena through alkylation of racemic α-methylbenzylamine with crotyl bromide, followed by DMAP-promoted acylation with methyl malonyl chloride to give **4a**, and manganic triacetate dihydrate/cupric acetate hydrate-induced radical cyclization (Scheme 2). Although the two diastereomers could be isolated by column chromatography, we employed the mixture of diastereomers for the next reaction, since the stereogenic centers at positions 3 and 4 are destroyed in the eventual conversion of this intermediate to a pyrrolopyrimidine. Pyrrolidinone **5a** was thiated with P_2S_5 in THF to give the thiolactam **6a** (68%), which was then converted in 50% yield with guanidine to the 5,6-dihydropyrrolo[2,3-*d*]pyrimidine **7a**. This appealing intermediate was then subjected to a standard Pd-catalyzed Heck reaction with diethyl 4-iodobenzoylglutamate.[6] To our surprise and pleasure, we found that the coupling product was not the anticipated vinyl-bridged pyrrolinopyrimidine **8a** but was the ethano-bridged pyrrolopyrimidine **9a** (68%). This unexpected double bond migration obviated our anticipated need for reduction of the unsaturated bridge of **8a** and subsequent oxidation of the pyrroline ring. Saponification of the glutamate esters[1a,4,6] with sodium hydroxide in aqueous THF then gave the 7-α-methylbenzyl derivative **10a** (82%).

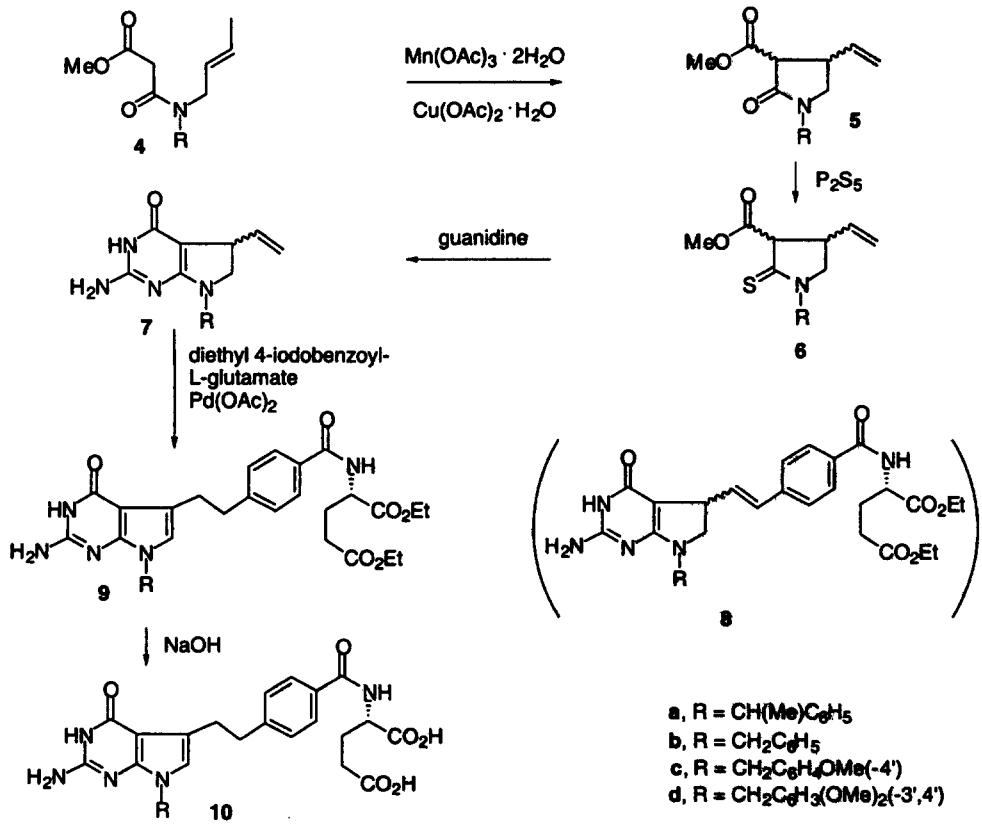


2 **3a** **3b**

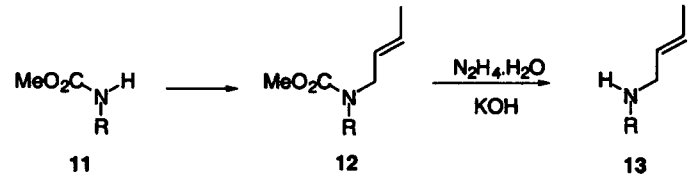
Scheme 1.

Several additional 7-substituted derivatives of **1** (e.g., 7-benzyl (**10b**), 7-(4′-methoxy)benzyl (**10c**) and 7-(3′,4′-dimethoxy)benzyl (**10d**)) were similarly prepared starting with the appropriate malonamides **4b–d**. However, the precursor crotyl amines **4b–d** proved in our hands impossible to prepare by direct alkylation of benzylamine, 4′-methoxybenzylamine and 3′,4′-dimethoxybenzylamine, respectively, with crotyl bromide, since dialkylation inevitably occurred. As a consequence, the above benzylamines were first acylated with methyl chloroformate (94, 96 and 94% yield, respectively), and the resulting carbamates **11b–d** were alkylated with crotyl bromide to give **12b–d** (96, 99 and 95% yield, respectively). These compounds were then converted to the desired secondary amines **13b–d** (86, 88 and 90% yield, respectively) with aqueous hydrazine and potassium hydroxide[7] (Scheme 3).

Extensive efforts were then made to remove the N-7 protecting groups from **9a–c**, but without any success. Deprotection of **9d** to **9** (R=H), however, was finally achieved in 30% yield with H_2SO_4/TFA



Scheme 2.



Scheme 3.

at room temperature[8] (rapid decomposition took place at higher temperatures). LY231514 (MTA, **1**) has previously been prepared from **9** (R=H) by saponification.[4]

In the course of extensive previous SAR studies on MTA, we had observed that *N*-substitution at position 7 eliminated cell growth inhibitory activity.[9] We were therefore surprised to see in a patent by Takeda Chemical Industries[10] the claim that a broad variety of 7-substituted derivatives of MTA (including **10a** and **10c**) were active antitumor agents. In confirmation of our earlier studies, we have found that these compounds are inactive (IC_{50}>20 μg/ml) as cell growth inhibitors.

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References

1. (a) 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. (b) Taylor, E. C.; Kuhnt, D.; Shih, C. In *Chemistry and Biology of Pteridines and Folates*; Pfleiderer, W.; Rokos, H., Eds.; Blackwell Science: Berlin, 1997; p. 81. (c) Shih, C.; Beardsley, G. P.; Chen, V. J.; Ehlhardt, W. J.; MacKellar, W. C.; Mendelsohn, L. G.; Ratnam, M.; Schultz, R. M.; Taylor, E. C.; Worzalla, J. F. In *Chemistry and Biology of Pteridines and Folates*; Pfleiderer, W.; Rokos, H., Eds.; Blackwell Science: Berlin, 1997; p. 181. (d) Thornton, D. E.; John, W.; Loeher, P.; Eisenhauer, E. In *Chemistry and Biology of Pteridines and Folates*; Pfleiderer, W.; Rokos, H., Eds.; Blackwell Science: Berlin, 1997; p. 195. (e) 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. (f) Calvert, A. H.; Walling, J. M. *British J. Cancer* **1998**, *78* (Suppl.), 35. (g) 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. (h) 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. (i) John, W.; Clark, J.; Burris, H.; Picus, J.; Schulman, L.; Thornton, D.; Lochrer, P. *Proc. Am. Soc. Clin. Oncol.* **1997**, *16*, 292a-A1038. (j) 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. (k) Rusthoven, J.; Eisenhauer, E.; Butts, C.; Gregg, R.; Dancey, J.; Fisher, B.; Iglesias, J. *Eur. J. Cancer* **1997**, *33* (Suppl. 8), S231-a1045. (l) Thoedtmann, R.; Kemmerich, M.; Depenbrock, H.; Blatter, J.; Ohnmacht, U.; Rastetter, J.; Hanauske, A. R. *Eur. J. Cancer* **1997**, *33* (Suppl. 8), S247-a1116.
2. 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.
3. Barnett, C. J.; Wilson, T. M.; Kobierski, M. E. In *Chemistry and Biology of Pteridines and Folates*; Pfleiderer, W.; Rokos, H., Eds.; Blackwell Science: Berlin, 1997; p. 123.
4. Taylor, E. C; Liu, B. *Tetrahedron Lett.* **1999**, *40*, in press.
5. Galeazzi, R.; Mobbili, G.; Orena, M. *Tetrahedron* **1996**, *52*, 1069.
6. See, for example: Taylor, E. C.; Jennings, L. D.; Mao, Z.; Hu, B.; Jun, G.-G.; Zhou, P. *J. Org. Chem.* **1997**, *62*, 5392.
7. Shono, T.; Matsumura, Y.; Uchida, K.; Tsubata, K.; Makino, A. *J. Org. Chem.* **1984**, *49*, 300. (b) Wee, A. G. H.; Liu, B.; Zhang, L. *J. Org. Chem.* **1992**, *57*, 4404.
8. Jones, M. I.; Froussios, C.; Evans, D. A. *J. Chem. Soc., Chem. Comm.* **1976**, 472.
9. Taylor, E. C.; Shih, C.; Gossett, L. S.; Meldelsohn, L. G., unpublished observations.
10. Akimoto, H.; Ootsu, K. Eur. Pat. Appl. 91-300266 910115.