Asymmetric Synthesis of Dideazafolate Antitumor Agents via Amidomethylation of Nonracemic Oxazolidinone Imidates. Synthesis of LY309887, a Cytotoxic Dideazafolate Analog Related to Lometrexol

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Abstract: The asymmetric synthesis of LY309887, a cytotoxic dideaza tetrahydrofolate analog related to lometrexol, has been accomplished via an application of diastereoselective amidomethylation of a chiral titanium (IV) acyloxazolidinone enolate. © 1997, Elsevier Science Ltd. All rights reserved.

The deazafoolate series has been found to be a rich source of folate antagonists which exhibit clinically useful levels of antitumor activity via inhibition of various folate requiring enzymes.1 Within this series, the 5,10-dideaza analogs of tetrahydrofolic acid, as exemplified by lometrexol (1a) have been found to exert very potent cytotoxic effects via specific inhibition of glycaminamide ribonucleotide formyl transferase (GARFT).1,2 More recently, LY309887 (1b), a thiophene analog of lometrexol, has been found to be substantially more active than lometrexol itself3 and to possess an improved therapeutic index when coadministered with folate.4 Phase I clinical evaluation of this new analog is currently in progress. The initial synthetic approach provided 1b as a mixture of C-6 epimers via sequential palladium(0) mediated coupling of acetylene with aryl halide and 5-deazapterin intermediates.5 The diastereomers were subsequently separated chromatographically and a configurational assignment of 6R for LY309887 was inferred from comparisons of HPLC retention times and hGARFT inhibition constants of the individual diastereomers with data from the corresponding diastereomers of lometrexol.3 We wish to report here an asymmetric synthesis of LY309887 which permits rational assignment of the R configuration to C-6.

\[
\text{1a} \quad X = \text{CH=CH} \\
\text{1b} \quad X = \text{S}
\]

The 5-arylethyl substituted 2-piperidone A (X = CH=CH) was a key subgoal for a previously described asymmetric synthesis of lometrexol6 and this strategy is clearly applicable to other analogs including LY309887 (1b). We have envisioned an new, alternative synthesis of compounds A from β-acylamino acid derivatives B via asymmetric amidalkylation of nonracemic acyloxazolidinones (as their titanium(IV)-derived imidates C) as indicated below. A prototypical example of this asymmetric amidomethylation process, involving reaction of N-chloromethylbenzamide with a titanium(IV) imidate of structure related to C, has
previously been reported.\(^7\) We have applied this methodology to the synthesis of LY309887 (1b) as shown in the following scheme.

\[(a) \text{BnBr, } K_2CO_3, \text{DMF}; (b) \text{chromic acid, } \text{H}_2\text{SO}_4, \text{acetone}; (c) \text{PivCl, Et}_3\text{N, THF, 0 °C}; (d) n-\text{BuLi, -70 °C}; (e) \text{TiCl}_4, \text{Ph}_2\text{NET, CH}_2\text{Cl}_2, -60 \rightarrow 0 °C; (f) \text{LiBH}_4, \text{THF, 0 °C}; (g) \text{MsCl, CH}_2\text{Cl}_2, \text{Et}_3\text{N}; (h) \text{diethyl malonate, NaH, THF (reflux)}; (i) \text{HBr, 30\% in HOAc}; (j) \text{P}_2\text{S}_5, \text{THF, 60 °C}; (k) \text{guanidine, 90 °C}; (l) 2-\text{chloro-4,6-dimethoxy-1,3,5-triazine, Et}_3\text{N, DMF}; (m) \text{aq NaOH; aq HCl}}\]
Preparation of the required acyloxadolidinone for LY309887 synthesis was carried out conventionally as indicated. The known acetal acid 2, prepared from dilithiated 5-methylthiophene-2-carboxylic acid by a literature procedure, was converted to its benzyl ester and then (without isolation) to thienylbutyric acid 4 upon exposure to Jones oxidation conditions (84% overall yield from 5-methylthiophene-2-carboxylic acid). Conversion of 4 to the (R)-4-benzoxadolidinone derivative was accomplished via reaction of the lithium salt of (R)-(+)-4-benzyl-2-oxazolidinone with the mixed pivalic anhydride (5) (not isolated) in 62% yield after chromatography.

Asymmetric amidomethylation was effected by reaction of the titanium enolate of 6 with a reagent prepared from N-methoxymethyl benzyl carbamate (7) and 1 equivalent of titanium(IV) chloride in methylene chloride at -60 °C, then warming to 0 °C, giving rise to Z-protected β-aminoacid derivative 8 in 76% yield after chromatography (d.e. >98%). The high level of asymmetric induction obtained in this process was anticipated from the earlier example. The absolute configuration of the new stereocenter in 8 was assigned as S on the basis of substantial precedent for the directing effect of the chiral oxazolidinone auxiliary in reactions of the corresponding enolates with electrophiles, including N-chloromethylbenzamidine. The N-methoxymethyl carbamate-based amidomethylation reagent was chosen over the more reactive N-chloromethylbenzamide in anticipation of the need to remove the acyl residue from the newly established aminomethylene group under mild conditions in the context of the synthesis. Attempted preparation of (presumably more reactive) N-chloromethyl benzyl carbamate via chlorination of N-hydroxymethyl benzyl carbamate was unsuccessful under a variety of conditions.

Reduction of 8 with lithium borohydride provided alcohol 9 in 74% yield along with the intact oxazolidinone chiral auxiliary which could be recycled. Activation of the primary hydroxyl group as the mesylate (10) and reaction with the sodium enolate of diethyl malonate gave the Z-protected aminodiester 11 in 69% overall yield from 9. Exposure of 11 to debenzylation conditions (HBr 30% in acetic acid, rt, 1h) followed by neutralization gave rise to the lactam acid 12 in 55% crystallized yield. Importantly, the thiophene and lactam carboxyl groups in 12 were now distinguished. Reaction of 12 with phosphorus pentasulfide in THF caused sulfurization of the lactam carbonyl group, providing 13 (47% yield after chromatography), which gave pteroic acid analog 14 in 70% yield upon reaction with hot guanidine. Coupling of 14 with diethyl L-glutamate after activation with 2-chloro-4,6-dimethoxy-1,3,5-triazine gave the diester 15 in 51% yield after recrystallization as the (-)-10-camphorsulfonate salt. No products resulting from acylation of the unprotected pyrimidine 2-amino group of either 14 or 15 were observed. Analysis of crude 15 (prior to camphorsulfonate crystallization) by HPLC using β-cyclodextrin as a chiral selector indicated that the C-6 epimeric ratio was >99.5:0.5, thus establishing the stereocchemical integrity of the sequence 8→15. Saponification of 15 followed by acidification afforded LY309887 (1b) as an amorphous solid identical in all respects, including β-cyclodextrin HPLC analysis, with an authentic sample obtained from the HPLC separation of a mixture of C-6 epimers of LY309887 which had been prepared by the literature method.
References and Notes


9. All new compounds have been characterized spectroscopically and by either elemental analysis or high resolution mass spectroscopy.


12. The titanium enolate of 5 was prepared in situ by reaction with 1.05 equiv of TiCl₄ and 1.05 equiv of i-Pr₂NEt in CH₂Cl₂ at -65 °C then warming to 0 °C according to the published procedure (ref 7).

13. Shono, S.; Matsumura, Y.; Tsubata, K. *Nippon Kagaku Kaishi* 1984, 11, 1782-1787; Chem. Abstr. 1985, 102, 61636h. We prepared 7 by sequential reaction of benzyl carbamate with formaldehyde and methanol/catalytic p-toluene sulfonic acid according to the following procedure. Benzyl carbamate (10.0 g, 66.1 mmol), 37% aq formaldehyde (6.20 g, 69.5 mmol), and K₂CO₃ (183 mg, 1.32 mmol) was combined in 75 mL of water and the rapidly stirred mixture was heated to 60 °C for 30 min. After addition of 30 mL of MeOH and cooling over 10 h the mixture was filtered and the isolated product was recrystallized from toluene to give 7.10 g (59%) of benzyl N-(hydroxymethyl)carbamate, mp 81.5-83.5 °C (lit 86.5-87.5 °C). A solution of 5.00 g (27.6 mmol) of the benzyl hydroxymethyl carbamate in 50 mL of CH₂Cl₂ was added 11.0 mL (8.84 g, 0.276 mmol) of anhydrous methanol and 100 mg of p-TsOH. The solution was stirred under N₂ at ambient temperature for 3 h and filtered through a plug of silica. Concentration gave 5.40 g (100%) of 7 as a colorless oil. ¹H NMR (250 MHz, CDCl₃) δ 7.36 (m, 5H), 5.53 (b, 1H), 5.14 (s, 2H), 4.63 (d J = 7.1 Hz, 2H), 3.34 (s, 3H).

14. HPLC of the crude product indicated that the reaction had proceeded with 96.4% d.e. Additional enhancement was obtained during chromatographic purification. Starting 5 representing a recovery of 21% was also obtained from the column.

15. The moderate yield of 13 appeared to be due in part to difficulties in eluting the material completely from the silica gel column.

16. Procedures for the sulfuration and guanidine cyclization reactions were essentially as described previously. See reference 6.


18. The preparative HPLC separation of the C-6 diastereomers of LY309887 was developed by Dr. C. Shih and coworkers, Lilly Research Labs.

(Received in USA 18 November 1996; accepted 4 December 1996)