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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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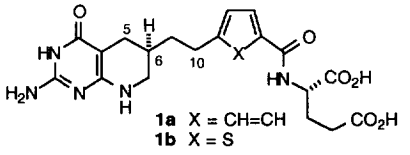
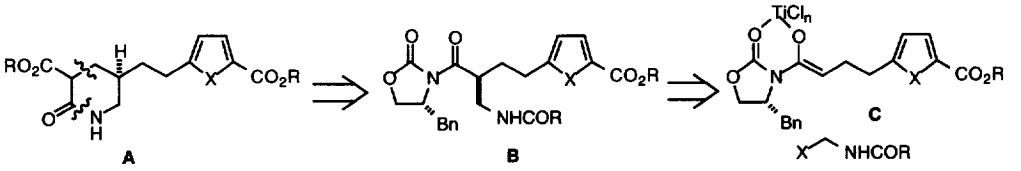
Abstract: The asymmetric synthesis of LY309887, a cytotoxic dideazatetrahydrofolate analog related to lometrexol, has been accomplished via an application of diastereoselective amidomethylation of a chiral titanium (IV) acyloxazolidinone enolate.

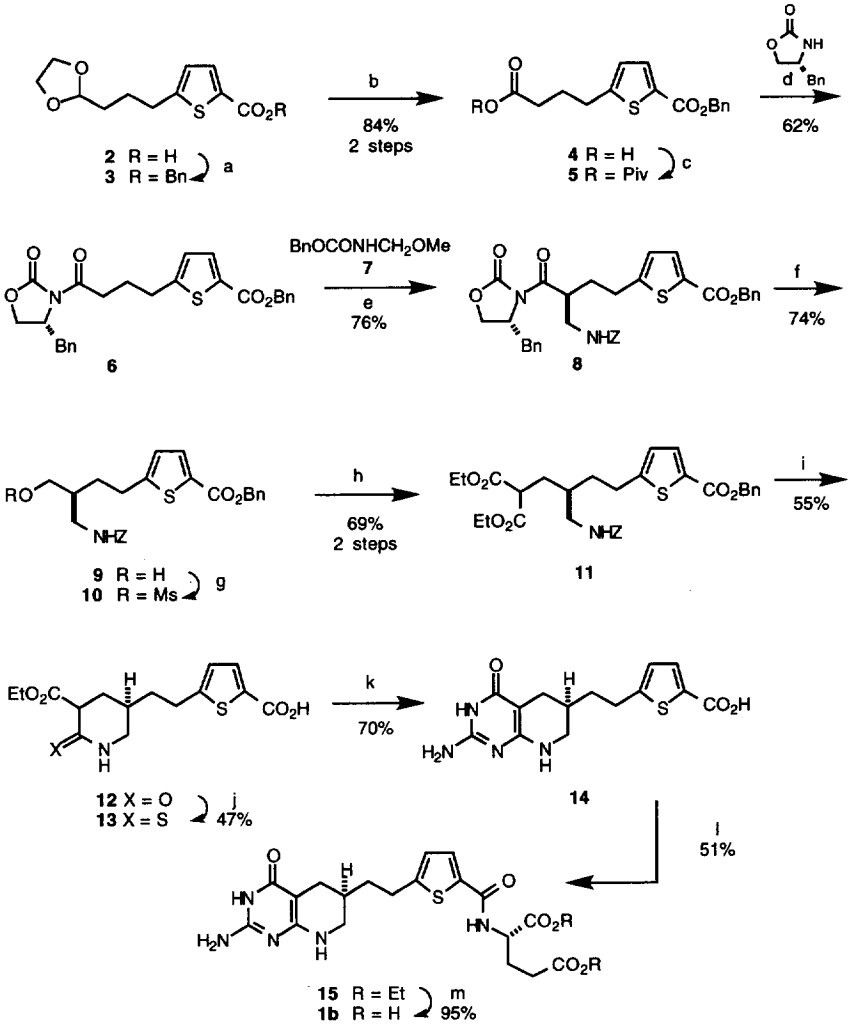
The deazafolate series has been found to be a rich source of folate antagonists which exhibit clinically useful levels of antitumor activity via inhibition of various folate requiring enzymes.[1] Within this series, the 5,10-dideaza analogs of tetrahydrofolic acid, as exemplified by lometrexol (**1a**) have been found to exert very potent cytotoxic effects via specific inhibition of glycinamide 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 itself[3] 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.



The 5-arylethyl substituted 2-piperidone **A** (X = CH=CH) was a key subgoal for a previously described asymmetric synthesis of lometrexol[6] 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 amidoalkylation 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) BnBr, K_2CO_3, DMF; (b) chromic acid, H_2SO_4, acetone; (c) PivCl, Et_3N, THF, 0 °C; (d) n-BuLi, -70 °C; (e) $TiCl_4$, *i*-PrNEt, CH_2Cl_2, -60 → 0 °C; (f) $LiBH_4$, THF, 0 °C; (g) MsCl, CH_2Cl_2, Et_3N; (h) diethyl malonate, NaH, THF (reflux); (i) HBr, 30% in HOAc; (j) P_2S_5, THF, 60 °C; (k) guanidine, 90 °C; (l) 2-chloro-4,6-dimethoxy-1,3,5-triazine, Et_3N, DMF; (m) aq NaOH; aq HCl

Preparation of the required acyloxazolidinone 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,[8] 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).[9] Conversion of **4** to the (*R*)-4-benzyloxadolidinone derivative was accomplished via reaction of the lithium salt of (*R*)-(+)-4-benzyl-2-oxazolidinone[10] with the mixed pivialic anhydride (**5**)[11] (not isolated) in 62% yield after chromatography.

Asymmetric amidomethylation was effected by reaction of the titanium enolate of **6**[12] with a reagent prepared from *N*-methoxymethyl benzyl carbamate (**7**)[13] 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%).[14] The high level of asymmetric induction obtained in this process was anticipated from the earlier example.[7] 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*-chloromethylbenzamide.[7] The *N*-methoxymethyl carbamate-based amidomethylating 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, 18h) 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 distingushed. Reaction of **12** with phosphorus pentasulfide in THF caused sulfurization of the lactam carbonyl group, providing **13** (47% yield after chromatography[15]), which gave pteroic acid analog **14** in 70% yield upon reaction with hot guanidine.[16] Coupling of **14** with diethyl L-glutamate after activation with 2-chloro-4,6-dimethoxy-1,3,5-triazine[17] gave the diester **15** in 51% yield after recrystallization as the (-)-10-camphorsulfonate salt. No products resulting from acylation of the unprotected pyrimidone 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 stereochemical 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[18] of LY309887 which had been prepared by the literature method.[5]

References and Notes

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12. The titanium enolate of **5** was prepared *in situ* by reaction with 1.05 equiv of $TiCl_4$ and 1.05 equiv of *i*-Pr_2NEt in CH_2Cl_2 at -65 °C then warming to 0 °C according to the published procedure (ref 7).
13. Shono, S.; Matsumura, Y; Tsubata, K. *Nippon Kagku 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*-toluenesulfonic acid according to the following procedure. Benzyl carbamate (10.0 g, 66.1 mmol), 37% aq formaldeyhde (6.20 g, 69.5 mmol), and K_2CO_3 (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 CH_2Cl_2 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 N_2 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, $CDCl_3$) 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 sulfurization and guanidine cyclization reactions were essentially as described previously. See reference 6.
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18. The preparative HPLC separation of the C-6 diastereomers of LY309887 was developed by Dr. C. Shih and coworkers, Lilly Research Labs.

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