by differences in solvent behavior between EtOD–D_2O and EtOH–H_2O. The 0.31-unit larger ΔpK for **2b** relative to **1b** is reasonable since **2b**·H^+ has *two* exchangeable hydrogens which are sterically inhibited from hydrogen bonding[21] and therefore exhibit high-frequency stretching vibrations. The 0.26-unit larger ΔpK for **3b** relative to **1b** must be due to exceptionally high bending frequencies for the exchangeable hydrogen in **3b**·H^+.[22]

Acknowledgment. We thank Professor R. W. Taft for helpful discussions and Mr. Ray Holsten for obtaining the gas-phase basicities.

(21) As before, the residual NH in neutral **2b** is expected to exert an opposite but much smaller effect.

(22) Assuming that the SIE contributions toward the ΔpK values of **1b** and **3b** are very similar and accounting for the relatively small difference in NH stretching frequency between **1b**·H^+ and **3b**·H^+, one can estimate that NH bending frequencies are about 1000 cm^{-1} larger for the latter ion than for the former.

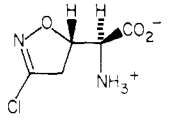
Stereospecific Total Syntheses of the Natural Antitumor Agent ($\alpha S,5S$)-α-Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic Acid and Its Unnatural C-5 Epimer

Richard B. Silverman*,† and Mark W. Holladay

Department of Chemistry, Northwestern University
Evanston, Illinois 60201

Received August 27, 1981

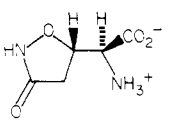
The antitumor[1] and enzyme-inhibitory[2] properties of the antimetabolite ($\alpha S,5S$)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT-125, **1a**) have prompted several reports on the



1a

total synthesis of **1a** and some analogues.[3] We wish to report here a short, efficient, and easily carried out stereospecific synthesis of **1a**, which also has been adapted to its C-5 epimer (**1b**).[4]

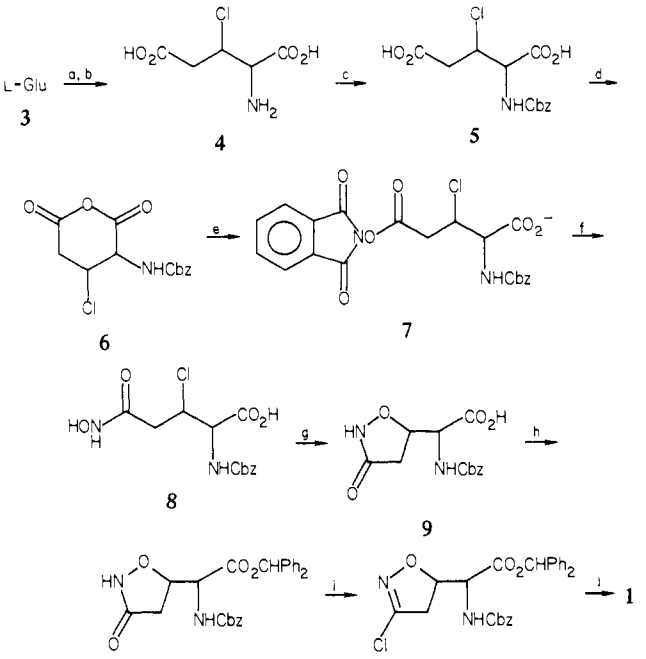
Our synthetic plan required an efficient means for the preparation of stereochemically pure derivatives of tricholomic acid (**2**).[5]



2

A key feature in the strategy to this end involved the photochlorination of L-glutamic acid (**3**) by the procedure of Kollonitsch et al.[6] (concentrated H_2SO_4, Cl_2, $h\nu$, 5 h), which afforded approximately a 1:1 mixture of the L-*threo*- and L-*erythro*-β-chloroglutamic acids, **4a**[7a] (mp 140 °C (dec)) and **4b**[8a] (mp 140.5 °C (dec)), respectively. These diastereomers were separated by ion-exchange chromatography (Dowex-50 (H^+), 0.1 N HCl) in a 33% overall yield based on recovered starting material. The pure isomers thus obtained were independently converted by the same series of reactions (Scheme I) to **1a** and **1b**, respectively. The following description for the conversion of **4a** to **1a** applies to the preparation of **1b** from **4b**, except where noted.

Scheme I. Synthetic Route to 1a and 1b[a]



[a] a, Cl_2, $h\nu$, H_2SO_4; b, Dowex-50 (H^+); c, benzyl chloroformate, pH 9; d, DCC, EtOAc, 0 °C; e, **12**, THF, −30 to −50 °C; f, aqueous NH_2OH; g, aqueous NEt_3, pH 11; h, Ph_2CN_2, THF; i, $Cl_2P(NMe_2)_3$, THF; j, CF_3CO_2H, PhSMe.

Treatment of **4a** with benzyl chloroformate at pH 9 afforded the Cbz-protected[9] derivative **5a**[7b] (85%, mp 144–144.5 °C; **5b**, 72%, mp 130–130.5 °C), which was converted to the cyclic anhydride **6a**[7c] (85%, mp 141–142.5 °C (dec); **6b**,[8c] 82%, mp 118.5–120 °C) with DCC in EtOAc at 0 °C.[10]

† Alfred P. Sloan Research Fellow, 1981–1983.

(1) Hanka, L. J.; Martin, D. G.; Neil, G. L. *Cancer Chemother. Rep.* **1973**, *57*, 141–148.

(2) (a) Jayaram, H. N.; Cooney, D. A.; Ryan, J. A.; Neil, G.; Dion, R. L.; Bono, V. H. *Cancer Chemother. Rep.* **1975**, *59*, 481–491. (b) Cooney, D. A.; Jayaram, H. N.; Ryan, J. A.; Bono, V. H. *Ibid.* **1974**, *58*, 793–802.

(3) (a) Kelly, R. C.; Schletter, I.; Stein, S. J.; Wierenga, W. *J. Am. Chem. Soc.* **1979**, *101*, 1054–1055. (b) Baldwin, J. E.; Kruse, L. I.; Cha, J. K. *Ibid.* **1981**, *103*, 942–943. (c) Hagedorn, A. A., III; Miller, B. J.; Nagy, J. O. *Tetrahedron Lett.* **1980**, *21*, 229–230.

(4) All compounds bearing the letter **a** indicate that they are on the pathway leading to natural ($\alpha S,5S$;L-*erythro*)-AT-125, whereas those bearing the letter **b** are on the pathway to unnatural ($\alpha S,5R$;L-*threo*)-AT-125.

(5) Kamiya, T. *Chem. Pharm. Bull.* **1969**, *17*, 890–894.

(6) (a) Kollonitsch, J.; Rosegay, A.; Doldouras, G. *J. Am. Chem. Soc.* **1964**, *86*, 1857–1858. (b) Kollonitsch, J. U.S. Patent 3 412 147 (1968) (cf. *Chem. Abstr.* **1965**, *62*, P4121*h*.

(7) ^1H NMR: (a) **4a** (CF_3CO_2H), δ 3.3 (d, J = 6 Hz, 2 H), 4.7–5.2 (m, 2 H); (b) **5a** (acetone-d_6), δ 2.8–3.0 (m, 2 H), 4.75–5.15 (m, 2 H), 5.1 (s, 2 H), 7.3 (s, 5 H); (c) **6a** (acetone-d_6) δ 2.75 (s, 1 H), 3.45 (m, 2 H), 4.8 (m, 2 H), 5.05 (s, 2 H), 7.25 (s, 5 H); (d) **8a**·NH_2OH (D_2O), δ 2.55 (m, 2 H), 4.3 (m, 1 H), 4.6 (HDO), 5.05 (s, 2 H), 7.35 (s, 5 H); (e) **8a**·**DCHA** ($CDCl_3$), δ 0.85–2.25 (m, 20 H), 2.55–3.25 (m, 4 H), 4.25 (m, 1 H), 4.7 (m, 1 H), 5.05 (s, 2 H), 6.05 (br d, J = 5 Hz, 1 H), 7.2 (s, 5 H), 8–9 (br s, 2 H); (f) **9a**·**DCHA** ($CDCl_3$), δ 0.85–2.3 (m, 20 H), 2.5–3.5 (m, 4 H), 4.25 (dd, J = 3, 6 Hz, 1H), 4.95 (m, 1 H), 5.1 (s, 2 H), 6.2 (br d, J = 6 Hz, 1 H); (g) **10a** (acetone-D_6), δ 2.75 (d, J = 7 Hz, 2 H), 4.6–4.9 (m, 2 H), 5.05 (s, 2 H), 6.8 (s, 1 H), 7.25 (s, 15 H); (h) **11a** ($CDCl_3$), δ 3.08 (d, J = 11 Hz, 1 H), 3.12 (d, J = 8 Hz, 1 H), 4.6 (dd, J = 4, 8 Hz, 1 H), 4.85–5.1 (m, 1 H), 5.05 (s, 2 H), 5.7 (br d, J = 8 Hz, 1 H), 6.8 (s, 1 H), 7.25 (s, 15 H).

(8) ^1H NMR: (a) **4b** (CF_3CO_2H), δ 3.3 (d, J = 7 Hz, 2 H), 4.7–5.2 (m, 2 H); (b) **5b** (acetone-d_6), δ 2.75–3.05 (m, 2 H), 4.55–4.85 (m, 2 H), 5.1 (s, 2 H), 7.35 (s, 5 H); (c) **6b** ($CDCl_3$), δ 3.4 (d, J = 3 Hz, 2 H), 4.65 (m, 1 H), 5.0 (dd, J = 3, 7 Hz, 1 H), 5.15 (s, 2 H), 5.8 (br d, J = 7 Hz, 1 H), 7.35 (s, 5 H); (d) **8b**·**DCHA** ($CDCl_3$), δ 0.85–2.3 (m, 20 H), 2.5–3.5 (m, 4 H), 4.3 (d, J = 5 Hz, 1 H), 4.8 (m, 1 H), 5.2 (s, 2 H), 6.2 (br d, J = 5 Hz, 2 H), 7.45 (s, 5 H); (e) **10b** (acetone-d_6), δ 2.75 (d, J = 9 Hz, 2 H), 4.7 (dd, J = 3, 9 Hz, 1 H), 5.0–5.35 (m, 1 H) 5.0 (s, 2 H), 6.85 (s, 1 H), 7.3 (s, 15 H); (f) **11b** (acetone-d_6), δ 3.15 (d, J = 10 Hz, 2 H), 4.6 (m, 1 H), 5.05 (s, 2 H), 5.25–5.6 (m, 2 H), 6.85 (s, 1 H), 7.25 (s, 15 H); (g) **1b** (D_2O), δ 3.4 (m, 2 H), 3.85 (m, 1 H), 5.1 (m, 1 H).

(9) Abbreviations used in this paper are are follows: Cbz = benzyloxycarbonyl; Boc = *tert*-butyloxycarbonyl; DCC = dicyclohexylcarbodiimide; DCHA = dicyclohexylamine.

(10) Earlier we had considered Boc to be a more favorable N-protecting group at this stage of the synthesis, but difficulties were encountered owing to the lower stabilities of L-*erythro*-*N*-Boc-β-chloroglutamic acid and, especially, of the corresponding anhydride, even under conditions significantly milder than those used to prepare the Cbz-protected analogues.

0002-7863/81/1503-7357$01.25/0

In the preparation of the γ-hydroxamic acid **8a** from the anhydride, it was desirable to minimize the formation of the corresponding α-hydroxamic acid. Nucleophiles are known to attack almost exclusively at the γ-carbonyl of *N*,*N*-phthaloylglutamic anhydride,[11] presumably for steric reasons. However, the phthaloyl protecting group could not be employed since conditions used for its incorporation into β-chloroglutamate led to elimination of HCl.[12] Consequently, model studies were undertaken to examine steric and electronic aspects of attack by several nucleophiles on various N-protected glutamic anhydrides. The reactions of *N*-(triphenylmethyl)- or *N*-Boc-glutamic anhydride with NH_2OH, NH_2OCH_2Ph, or NH_2OCPh_3 under a variety of temperature and solvent conditions yielded unacceptable mixtures of α and γ isomers. The reaction of the Boc-anhydride with $PhSH/NEt_3$ in THF, followed by NH_2OH,[13] proceeded with a high degree of preference for the desired γ-hydroxamic acid; however, these conditions were too severe for the corresponding Boc-β-chloroglutamic anhydride, even at lower temperatures and when NEt_3 was replaced by the more hindered NEt-*i*-Pr_2. On the basis of a hypothesis that an anionic nucleophile had a stronger preference for the γ rather than the α carbonyl,[14] a charged nucleophile which also would be a good leaving group for displacement by NH_2OH was sought. The lithium salt of *N*-hydroxyphthalimide (**12**) was found to be quite effective and showed an overwhelming preference for attack at the γ-carbonyl moiety of Boc- and Cbz-protected anhydrides. Furthermore, the product of this reaction (**7**) could be smoothly converted to the γ-hydroxamic acid with aqueous hydroxylamine. Analogous reactions with *N*-hydroxyphthalimide or PhSLi in place of **12** were less satisfactory. Thus, the reaction of **6a** with **12** in THF at −30 to −50 °C led to precipitation of **7**, which was not purified but was treated directly with a concentrated (~4 M) aqueous solution of hydroxylamine at pH 6 to afford **8a**·NH_2OH[7d] (mp 123.5–125 °C (dec)), which precipitated from the reaction mixture, and **8a**·DCHA[7e] (mp 119–120 °C (dec)), obtained after extractive workup followed by addition of DCHA, in a 66% combined overall yield from **6a**. The salts of **8a** were allowed to cyclize (NEt_3, pH 11, room temperature) via the free acid to Cbz-trichlolomic acid (**9a**) (foam; DCHA salt,[7f] mp 163–168 °C (dec)), which was treated with diphenyldiazomethane[15] to afford **10a**[7g] (foam; 74%, after chromatography, from **8a** salts).

The diastereomeric (L-*threo*) diprotected tricholomic acid **10b** was prepared from the anhydride **6b** by the same series of reactions as for the natural isomer except that the conversions were performed on unpurified or partially purified (i.e., extractive workup) intermediates because of the failure of intermediates **7b** and **8b**·NH_2OH to precipitate from the reaction mixtures. The overall yield for the four steps leading to pure **10b**[8e] (mp 161–162 °C) after chromatography was 46%. For analytical purposes, **8b** was characterized as the DCHA salt[8d] (mp 147–149 °C (dec)).

The natural diprotected tricholomic acid **10a** was converted to **11a**[7h] (mp 113–115 °C) with excess dichlorotris(dimethylamino)phosphorane[15] in refluxing THF[16] in a 54% purified yield. Removal of the Cbz and benzhydryl protecting groups was effected simultaneously in trifluoroacetic acid containing 8 equiv of thioanisole[17] to afford natural **1a** (87%) which was in all respects identical with the natural material.[18] Unnatural **1b**[8g] was prepared from **10b** in an analogous fashion in a 57% yield for the last two steps. The integrity of the chiral centers at each major stage in the syntheses and the stereospecificity of the isoxazole ring-forming reactions were demonstrated by deprotection followed by high-voltage paper electrophoresis (pH 1.9, 4.2 kV) of the resulting amino acids, which showed that pertinent intermediates were free from diastereomeric impurities.

The synthesis of **1a** reported here was carried out in eight steps from **4a** in a 17% overall yield (**1b** from **4b**, 15%).[19] Moreover, the required starting materials and reagents are commercially available or readily prepared, and most are quite inexpensive, especially in the early stages of the synthesis. The procedural manipulations are simple and three of the reactions are carried out in aqueous media; only one step from **4**, the formation of **10a**, requires chromatography.

Acknowledgment. We are grateful to Dr. David G. Martin (Upjohn Co.) for a generous donation of natural AT-125 (U-42,126), to Dr. Wendell Wierenga (Upjohn Co.) for experimental details of certain related reactions, and to the National Institutes of Health (Grant CA 21156) and the Research Corp. for financial support.

(11) (a) King, F. E.; Kidd, D. A. A. *J. Chem. Soc.* **1949**, 3315–3319. (b) King, F. E.; Jackson, B. S.; Kidd, D. A. A. *Ibid.* **1951**, 243–246.

(12) L-*threo*-*N*,*N*-Phthaloyl-β-(mesyloxy)-γ-(hydroxamido)glutamic acid also has been shown to cyclize nonstereospecifically to a mixture of diastereomers of DL-*N*,*N*-phthaloyltricholomic acid: Wierenga, W., private communication.

(13) Wieland, T.; Weidenmüller, H. L. *Justus Liebigs Ann. Chem.* **1955**, *597*, 111–122.

(14) When *erythro*-*N*-Boc-β-chloroglutamic anhydride was treated with PhSH followed by NH_2OCPh_3, and deprotected, a 1:1 mixture of γ-hydroxamate/α-hydroxamate was obtained; when PhSH/NEt-*i*-Pr_2 was used, no α-hydroxamate was observed, but the yield of γ-hydroxamate was low.

(15) Appel, R.; Schöler, H. *Chem. Ber.* **1977**, *110*, 2382–2384.

(16) Experimental details for a related reaction were kindly provided to us by Dr. W. Wierenga of Upjohn Co., for which we are very grateful.

(17) Kiso, Y.; Ukawa, K.; Akita, T. *J. Chem. Soc., Chem. Commun.* **1980**, 101–102.

(18) The synthetic material was identical with AT-125 (kindly donated by Dr. David Martin of Upjohn Co.) by NMR, IR, MS, ORD, high-voltage electrophoresis, and TLC (20:5:1) MeOH/H_2O/pyridine); $[\alpha]^{22}_D$ +148° (*c* 8.45 mg/mL, H_2O). For **1b**: IR (KBr) 891, 1363, 1395, 1515, 1590, 1605 cm^{-1}; $[\alpha]^{22}_D$ −109° (*c* 11.2 mg/mL, H_2O).

(19) Unless otherwise noted, satisfactory analyses for all elements except O were obtained for the following compounds: **4a**, **5a**, **6a**, **8a**·NH_2OH·H_2O, **10a**, **11a**, **1b**, **4b**, **5b**, **6b**, **8b**-DCHA (H, N, Cl), **10b**, **11b**.

Structures of Titanacyclobutanes

J. Bosco Lee, Gregory J. Gajda, William P. Schaefer, Thomas R. Howard, Takao Ikariya, Daniel A. Straus, and Robert H. Grubbs*

Contribution No. 6483 from the Laboratories of Chemistry California Institute of Technology Pasadena, California 91125

Received July 16, 1981

It has become apparent that the fundamental step of olefin metathesis[1] and other related catalytic reactions[2] involves equilibration between metal–alkylidene and metallacyclobutanes.[3-5] Although many of the structural features of metal–alkylidene species are established,[3] similar data are not available for metallacyclobutanes which undergo this important reaction. Two important structural parameters relating to catalytic reactions are the conformation of the ring and the ease of distorting the ring toward potential reactive intermediates. The degree of puckering

(1) Grubbs, R. H. *Prog. Inorg. Chem.* **1979**, *24*, 1. Grubbs, R. H.; Hoppin, C. *J. Am. Chem. Soc.* **1979**, *101*, 1499.

(2) Metallacyclobutanes have also been invoked as key intermediates in hydrocarbon cracking and isomerization reactions and olefin polymerization. Dartigues, J. M.; Chambellan, A.; Gault, F. G. *J. Am. Chem. Soc.* **1976**, *98*, 856. Foger, K.; Anderson, J. R. *J. Catal.* **1978**, 54, 318. Ivin, K. J.; Rooney, J. J.; Stewart, C. D.; Green, M. L. H.; Mahtab, R. *J. Chem. Soc., Chem. Commun.* **1978**, 604. Parshall, G. W.; Herskovitz, T.; Tebbe, F. N.; English, A. D.; Zeile, J. V. In "Fundamental Research in Homogeneous Catalysis"; Tsutsui, M., Ed.; Plenum Press: New York, 1979; Vol. 3.

(3) (a) Wengrovius, J. H.; Schrock, R. R.; Churchill, M. R.; Wissert, J. R.; Youngs, W. J. *J. Am. Chem. Soc.* **1980**, *102*, 4515. (b) Schrock, R. R.; Rocklage, S.; Wengrovius, J. H.; Rupprecht, G.; Fellman, J. *J. Mol. Catal.* **1980**, *8*, 73.

(4) (a) Tebbe, F. N.; Parshall, G. W.; Reddy, G. S. *J. Am. Chem. Soc.* **1978**, *100*, 3611. (b) Tebbe, F. N.; Parshall, G. W.; Ovenall, D. W. *Ibid.* **1979**, *101*, 5074. (c) Tebbe, F. N.; Harlow, R. L. *Ibid.* **1980**, *102*, 6151.

(5) Howard, T. R.; Lee, J. B.; Grubbs, R. H. *J. Am. Chem. Soc.* **1980**, *102*, 6876. This reaction has been found to be very general.

0002-7863/81/1503-7358$01.25/0