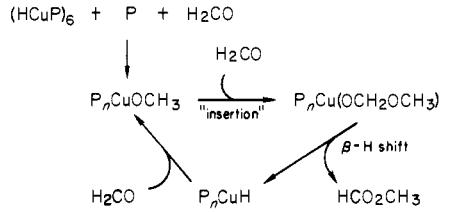
$$(1/6)(HCuP)_6 + H_2CO \rightarrow (1/n)(PCuOCH_3)_n \quad (3)$$

troscopy) that all of the deuterium in the methyl formate product in reaction 4 is found in the methyl group. We propose the

$$H_2CO \xrightarrow{(DCuP)_6} \underset{\text{(stoichiometric)}}{HCO_2CH_2D} + \underset{\text{(catalytic)}}{HCO_2CH_3} \quad (4)$$

following mechanism which accounts for this labeling result and employs an isoelectronic substitution (O for CH_2) in standard organometallic reaction types.



Consistent with cycles of this type, and consistent with the intermediacy of an alkoxide in the cycle, it is possible to enter the cycle from a nonhydride source[18] (reaction 5). The major points

$$(t\text{-BuOCuPPh}_3)_4{}^{20} + (H_2CO)_x \rightarrow \underset{\text{(stoichiometric)}}{HCO_2\text{-}t\text{-Bu}} + \underset{\text{(catalytic)}}{HCO_2Me} \quad (5)$$

to be drawn from this set of observations are that a well-defined soluble copper hydride does rapidly add to an aldehydic C=O bond and that it appears to do so to form a Cu–O, rather than a Cu–C bond. As a consequence of this latter selectivity, chain growth by CO insertion into metal–carbon bonds is precluded; this accounts for the selectivity for C_1 product exhibited by the Cu/Zn/oxide catalyst.[21]

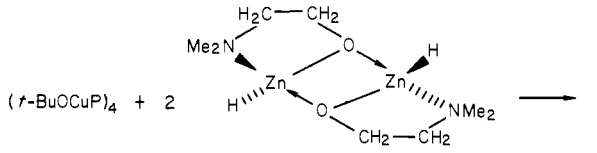
Treatment of a THF solution of $(CuO\text{-}t\text{-Bu})_4$ containing 2 mol of P per copper with H_2 (1 atm, 25 °C) gives 60% isolated yield of $(HCuP)_6$ after 4 h; the reaction also occurs in a nonpolar solvent (benzene) and shows somewhat higher yields (80%) using 1500 psi of H_2. Vacuum transfer of the volatiles from this reaction allows detection of both resonances of Me_3COH, verified by subsequent addition of an authentic sample of this alcohol. This reaction (reaction 6), the first "hydrogenolysis" of the metal-

$$(1/4)(CuO\text{-}t\text{-Bu})_4 + P + H_2 \rightarrow (1/6)(HCuP)_6 + t\text{-BuOH} \quad (6)$$

alkoxide bond in a soluble complex,[24] is the analogue of the final step in a methanol synthesis, and it is the step which has been lacking in previous work with the early transition metals. The production of a metal hydride from a metal alkoxide is a new synthetic procedure and indeed confirms a proposed[25] unique characteristic of copper: formal heterolytic splitting of hydrogen (reaction 7).[26]

$$Cu^+ + H_2 \rightarrow CuH + H^+ \quad (7)$$

In view of the proposal[9,10] that the commerical methanol catalyst involves reaction of a copper carbonyl with a zinc hydride, we have carried out a simple test of the relative stability of copper and zinc hydrides. The equimolar reaction of ZnH_2 with $HO(CH_2)_2NMe_2$ gives a complex of empirical formula $HZnO(CH_2)_2NMe_2$,[27] which we take to be a dimer by analogy to $[HZnNMe(CH_2)_2NMe_2]_2$.[28] Reaction in benzene according to reaction 8 gives rapid and complete hydride transfer from zinc



$$\tfrac{4}{6}(HCuP)_6 + 4Zn(Ot\text{-Bu})[O(CH_2)_2NMe_2] \quad (8)$$

to copper. We are continuing to devise further bimetallic reactions which even more faithfully mimic the environment of heterogeneous Cu/Zn/oxide catalysts. However, the solution result in reaction 8, coupled with the high mobility of ligated hydrogen in metal cluster compounds, suggests that the site of H–H bond *scission* may differ substantially from the site of hydrogen *transfer* to bound CO, both in physical location and in the identity of the metal atom which supplies the hydride.

Acknowledgment. This work was supported by NSF Grant CHE 80-06331. We thank Brad Basinger for the ^2H NMR spectra and Indiana University for a Grant-in-Aid of Research.

(20) Tsuda, T.; Habu, H.; Horiguchi, S.; Saegusa, T. *J. Am. Chem. Soc.* **1974**, *96*, 5930.

(21) Methyl formate is produced in homogeneously catalyzed CO hydrogenation reactions employing both $HCo(CO)_4$[16,22] and $Ru(CO)_5$.[23] The intermediacy of methoxide ligands and the operation of a Tishchenko reaction merits consideration in these cases.

(22) Rathke, J. W.; Feder, H. *J. Am. Chem. Soc.* **1978**, *100*, 3623.

(23) Bradley, J. S. *J. Am. Chem. Soc.* **1979**, *101*, 7419.

(24) Heterolysis of H_2 by metal acetates has been reported: White C.; Oliver, J. P.; Maitlis, P. M. *J. Chem. Soc., Dalton Trans.* **1973**, 1901.

(25) For Cu(II), see: Halpern, J.; Peters, E. *J. Chem. Phys.* **1955**, *23*, 605. For Cu(I), see: Hahn, E. A.; Peters, E. *J. Phys. Chem.* **1965**, *69*, 547. For a review, see: James, B. R. "Homogeneous Hydrogenation"; Wiley: New York, 1973; Chapter II.

(26) For a review of heterolytic activation of H_2, see: Brothers, P. J. *Prog. Inorg. Chem.* **1981**, *28*, 1. This review points out the difficulty of discriminating between heterolytic stoichiometry and a heterolytic mechanism; in the latter, the emerging H^+ never coordinates to the metal.

(27) This compound is nonrigid at an intermediate rate at 30 °C and thus shows broad ^1H NMR resonances. At 55 °C, the spectrum sharpens to reveal a hydride resonance at δ 4.20 (s, 1 H), methylene resonances at δ 4.00 (t, 2 H) and 2.50 (t, 2 H), and a methyl resonance at δ 2.23 (s, 6 H).

(28) Bell, N. A.; Moseley, P. T.; Shearer, H. M. M.; Spencer, C. B. *Acta Crystallogr., Sect. B* **1980**, *B36*, 2950.

Severe Steric Hindrance: Hydrogen Bonding and the Consequences of Its Inhibition. Equilibrium Hydrogen Isotope Effects

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The effect upon proton transfer equilibria of severe steric hindrance was first observed by Brown and Kanner, who synthesized 2,6-di-*tert*-butylpyridine (**1b**) and determined that, unlike other alkylated pyridines which were more basic than pyridine (**1a**) itself, **1b** was 0.80 p*K* units less basic than the latter (in 50 vol % aqueous ethanol).[1] Gas-phase basicity measurements[2] later showed that **1b** was intrinsically *more* basic than **1a** by more than 10 kcal/mol,[3] proving that solvation effects (inhibited H bonding[4]) were responsible for the observed anomaly. The remarkable observation[2a] that **1b**·H^+ shows solution behavior like that of resonance-stabilized carbocations and unlike that of ammonium ions was soon followed by studies dealing with the solution and gas-phase thermodynamics of **1b** and **1b**·H^+ and other pyridines and pyridinium ions.[5]

The availability of *cis*-2,6-di-*tert*-butylpiperidine[6] (**2b**) and the even more severely hindered *cis*-2,6-di-*tert*-butyl-*N*-methylpiperidine[7] (**3b**) made it of interest to determine the equilibrium

(1) Brown, H. C.; Kanner, B. *J. Am. Chem. Soc.* **1953**, *75*, 3895. *Ibid.* **1966**, *88*, 986.

(2) (a) Wolf, J. F.; Harch, P. G.; Taft, R. W. *J. Am. Chem. Soc.* **1975**, *97*, 2904. (b) Aue, D. H.; Webb, H. M.; Bowers, M. T.; Liotta, C. L.; Alexander, C. J.; Hopkins, H. P. *Ibid.* **1976**, *98*, 854.

(3) At 25 °C 1.00 p*K* unit corresponds to 1.36 kcal/mol.

(4) Arnett, E. M.; Chawla, B. *J. Am. Chem. Soc.* **1978**, *100*, 214, 217.

(5) (a) le Nobel, W.; Asano, T. *J. Org. Chem.* **1975**, *40*, 1179. (b) Hopkins, H. P.; Ali, S. Z. *J. Am. Chem. Soc.* **1977**, *99*, 2069. (c) Arnett, E. M.; Chawla, B. *Ibid.* **1979**, *101*, 7141.

(6) Day, J. C. *J. Org. Chem.* **1978**, *43*, 3646.

(7) Base **3b** is produced by reaction of **2b** with $CH_3OSO_2CF_3$. Details and characterization will be reported elsewhere.

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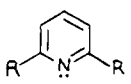
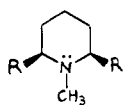


1a, R = H
b, R = *t*-Bu

2a, R = H
b, R = *t*-Bu
c, R = CH_3



3a, R = H
b, R = *t*-Bu

Figure 1.

Table I. Acidities of Ammonium and Pyridinium Ions in Ethanol–H_2O, Ethanol-*O*-*d*–D_2O, and H_2O. Gas-Phase Basicities

base	gas-phase basicity[a]	pK_a of BH^+ H_2O[b]	EtOH–H_2O[c,d]	EtOD–D_2O[c–e]	ΔpK[f]
1a	17.7	5.22	3.69	4.13	0.44
1b	28.7		2.70	2.92	0.22
2a	22.3	11.12	9.90	10.33	0.43
2b	30.8		7.09	7.62	0.53
3a	26.8	10.08, 10.19	8.61	9.01	0.40
3b	35.7		7.87	8.35	0.48

[a] Relative to NH_3: $-\Delta G$ (kcal/mol) for $NH_4^+ + B \rightleftharpoons NH_3 + BH^+$. [b] Lit: Perrin, D. D. "Dissociation Constants of Organic Bases in Aqueous Solution"; Butterworths: London, 1965. [c] Mole percent ethanol, 51.9 (73.4 wt % EtOH and 71.7 wt % EtOD, respectively). This solvent ratio allowed calibration of the Radiometer PHM 26 pH meter with standard buffers in 73.4% ethanol–water: See Bates, R. G.; Paabo, M.: Robinson, R. A. *J. Phys. Chem.* **1963**, *67*, 1833. [d] Determined by titration at 25.0 ± 0.3 °C of 0.0100 M BH^+ as BF_4^- (1b, 2b, 3b) or picrate (1a, 2a, 3a) with 0.0500 M NaOH containing 0.0100 M NaCl for maintenance of constant ionic strength. All salts were recrystallized to constant melting point. Syringe techniques were employed. Ionic strength corrections presumed a dielectric constant of 36.0. Reported pK_a values are averages of three titrations with agreement to ±0.02 pK unit in each case. [e] Values include 0.41 pH unit added to meter readings in EtOD–D_2O (see text). Isotopic enrichment was 99.5% (EtOD) and 99.8% (D_2O). [f] pK_a(EtOD–D_2O) − pK_a(EtOH–H_2O).

basicities of these new species. We now report that in EtOH–H_2O (mol % ethanol, 51.9) **1b** is 0.99 pK units less basic than pyridine (**1a**), **2b** is 2.81 pK units less basic than piperidine (**2a**), and **3b** is 0.74 pK units less basic than *N*-methylpiperidine (**3a**) (Table I). *Thus the addition of the flanking tert-butyl groups reduces the basicity of pyridine by a factor of 10 but the same structural feature reduces the basicity of piperidine some 650 times.* The dramatic reduction in the basicity of secondary amine **2b** seems only attributable to its conjugate acid (**2b**·H^+) having *both* acidic hydrogens sterically inaccessible to solvent **H** bonding: Gas-phase basicity measurements (pulsed ICR[8]) show that **1b**, **2b**, and **3b** are intrinsically *more* basic that **1a**, **2a**, and **3a** by 11.0, 8.5, and 8.9 kcal/mol, respectively (Table I). The NH stretching regions in the IR spectra of **2b** and **3b** in trifluoroacetic acid show only sharp, very weak peaks at 3300 and 3255 cm^{-1} for **2b**·H^+ and **3b**·H^+, respectively.[9] In contrast, the conventionally hindered amine 1,2,2,6,6-pentamethylpiperidine[10] (**4**) shows only the usual broad, intense absorption in TFA solution (at about 2500 cm^{-1}). These results strongly support the observation that "...the number and type of hydrogen bonds which an onium ion can donate to a basic solvent is a rough first-order guide to its solvation behavior."[11]

The effect upon intrinsic basicity of the two *tert*-butyl groups, though highly attenuated by solvent, substantially reduces the opposing desolvation effect in **1b**·H^+ and **3b**·H^+ but is overwhelmed in the case of **2b**·H^+ since the latter ion has two blocked hydrogen bonds rather than one.[12] The inhibition of hydrogen bonding in neutral secondary amine **2b**[6] presumably plays a much smaller role[11,13] in the base-strengthening direction for this hindered base.

In contrast to the usual "anomalous" order of amine basicities ($NH_3 < RNH_2 \approx R_2NH > R_3N$), **3b** is 0.78 p$K$ unit more basic than **2b**. Since hydrogen bonding is sterically inhibited to both **2b**·H^+ and **3b**·H^+, *there is no difference in the number of H bonds*[14] to the two cations and the intrinsic basicity order is followed. The 51.9 mol % ethanol exhibits normal "water-like" solvation effects on amine basicities: Cation **2c**·H^+ (pK_a = 9.89) is just as acidic as **2a**·H^+, and sterically congested **4**·H^+ (pK_a = 9.54) is about one pK unit less acidic than expected for a tertiary ammonium ion as it is in water.[15] Although *n*-Bu_3NH^+ (pK_a = 8.56) is structurally different from all other species studied and larger than **3a**·H^+, intrinsic basicity differences and large solvation effects cancel, leaving the two ions with very similar acidities.[16]

Basicities were determined in EtOD–D_2O (mol % ethanol-*O*-*d*, 51.9) with the expectation that **1b**, **2b**, and **3b** would show increased basicity toward deuterium since their conjugate acids show high NH stretching frequencies. Assuming for **1b**·H^+ an increase of at least 500 cm^{-1} relative to **1a**·H^+, one can readily calculate[17,18] that this effect should cause ΔpK to be at least 0.15 unit *larger* for **1b** than for **1a**. However, **1b** has a 0.22-unit *smaller* incremental preference for deuterium than does **1a** (only *differences among ΔpK values*[19] are of concern here). Hindered amines **2b** and **3b** show changes in the anticipated direction but the differences in ΔpK values relative to **2a** and **3a** are only 0.10 and 0.08 unit, respectively. The most likely explanation for these observations is a solvent isotope effect (SIE) due to the much greater hydrocarbon content of the three severely hindered species. If so, the addition of the two *tert*-butyl groups gives rise to a substantially larger incremental free energy of transfer from EtOH–H_2O to EtOD–D_2O for the bulky ammonium salts than for the hindered neutral bases.[20] A specific solvation effect for aromatic **1b**·H^+ leading to the uniquely small ΔpK of 0.22 cannot be ruled out. However Taft and co-workers have shown that **1b**·H^+ exhibits aqueous solvation energy very much like that of delocalized aryl carbocations, tetra-*n*-butylammonium, and tetraphenylphosphonium ions, all of which appear to show only general solvation effects and to lack "chemical" solvation at specific atomic sites.[2a] It appears, then, that the three ΔpK values are *all* reduced

(8) Wolf, J. F.; Staley, R. H.; Koppel, I.; Taagepera, M.; McIver, R. T., Jr.; Beauchamp, J. L.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 5417.

(9) A 3:1 mole ratio of TFA to each amine was used. Raman spectra of the crystalline HBF_4 salts show clear, sharp peaks at 3373 cm^{-1} (**1b**·H^+), 3303 and 3127 cm^{-1} (**2b**·H^+), and 3258 cm^{-1} (**3b**·H^+).

(10) Sommer, H. Z.; Lipp, H. I.; Jackson, L. L. *J. Org. Chem.* **1971**, *36*, 824.

(11) Arnett, E. M.; Chawla, B.; Bell, L.; Taagepera, M.; Hehre, W. J.; Taft, R. W. *J. Am. Chem. Soc.* **1977**, *99*, 5729.

(12) The same effect may be responsible for bis(3-ethyl-3-pentyl)amine being 2.8 pK units less basic than bis(2-methyl-2-butyl)amine in 90% ethanol (Kopke, I. E.; Fataftah, Z. A.; Rathke, M. W. *J. Org. Chem.* **1980**, *45*, 4616.

(13) Taagepera, M.; DeFrees, D.; Hehre, W. J.; Taft, R. W. *J. Am. Chem. Soc.* **1980**, *102*, 424.

(14) Trotman-Dickenson, A. F. *J. Chem. Soc.* **1949**, 1293.

(15) Aqueous pK_a values for **2c**·H^+ and **4**·H^+ are 11.07 and 11.19, respectively (Table I, footnote *b*).

(16) Amine **3a** is soluble in water but *n*-Bu_3N is not.

(17) Translational and rotational (and librational) effects may be neglected for these species. See: More O'Ferrall, R. A. In "Proton-Transfer Reactions"; Caldin, E. F., Gold, V., Eds.; Chapman and Hall: London, 1975; Chapter 8.

(18) The NH stretching frequency of **1b**·H^+ varies only from 3275 (**1b**·2TFA) to 3380 cm^{-1} (**1b**·*n*HF): see ref 5c. The corresponding frequency for **1a**·H^+ in hydroxylic media is far less certain (Katritzky, A. R.; Ambler, A. P. "Physical Methods in Heterocyclic Chemistry"; Katritzky, A. R., Ed.; Academic Press: New York, 1963; Vol. 2, pp 187, 274 ff). Values of 2400 and 2700 cm^{-1}, based on IR spectra of various pyridinium salts have recently been employed in theoretical calculations (Jasinski, J. M.; Brauman, J. I. *J. Am. Chem. Soc.* **1980**, *102*, 2906).

(19) All pK_a values in EtOD–D_2O were calculated by using the untested assumption that the pH electrode responds to deuterium in the mixed solvent as it does in pure D_2O: An increment of 0.41 was added to each meter reading in EtOD–D_2O: See: Covington, A. K.; Paabo, M.; Robinson, R. A.; Bates, R. G. *Anal. Chem.* **1968**, *40*, 700. Literature values for 16 ammonium salts (D_2O vs. H_2O) range from ΔpK = 0.48 to 0.63 units (Laughton, P. M.; Robertson, R. E. In "Solute-Solvent Interactions"; Coetzee, J. F., Ritchie, C. D., Eds.; Marcel Dekker: New York, 1969). The somewhat lower ΔpK values of 0.40–0.44 for **1a**, **2a**, and **3a** in the mixed solvent may reflect real differences in solvent behavior or may be an artifact of the above assumption.

(20) This is qualitatively consistent with solubility data for nonelectrolytes having no exchangeable hydrogens, which show only small differences in solubility between H_2O and D_2O and data for the bulky cation *n*-Bu_4N^+, which shows reduced solubility in D_2O relative to H_2O: Albery, J. In ref 17, Chapter 9.

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 (αS,5*S*)-α-Amino-3-chloro-4,5-dihydro-5-isoxazoleacetic Acid and Its Unnatural C-5 Epimer

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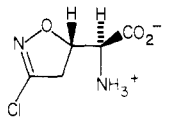
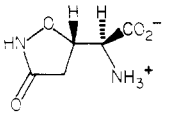
The antitumor[1] and enzyme-inhibitory[2] properties of the antimetabolite (αS,5*S*)-α-amino-3-chloro-4,5-dihydro-5-isoxazoleacetic acid (AT-125, **1a**) have prompted several reports on the



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]

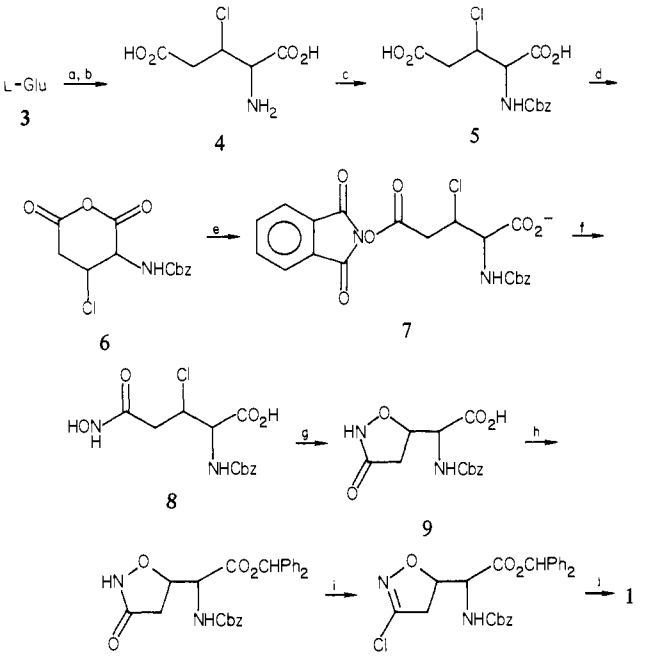
Our synthetic plan required an efficient means for the preparation of stereochemically pure derivatives of tricholomic acid (**2**).[5]



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, *hν*, 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, *hν*, 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.

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

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(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.

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