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Syntheses of Functionalized β-Lactams from Tartaric Acid

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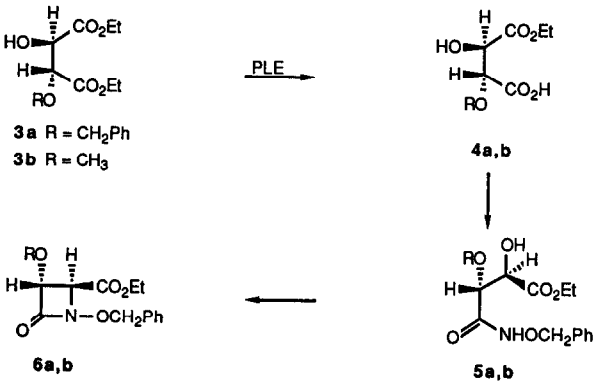
Summary: A totally chemical method has been developed to differentiate the hydroxyl and carboxyl groups of tartaric acid. Structural assignment of the resulting isomers has been unambiguously determined and the appropriate β-hydroxy-hydroxamate derivative has been converted cleanly to the corresponding β-lactam. Interestingly, the isomeric α-hydroxy-hydroxamate derivative could also be converted to the same β-lactam in modest yield.

Introduction

Tartaric acid **1** is a convenient and highly functionalized four carbon component for asymmetric synthesis. While it has received considerable attention recently as a chirality transfer agent, especially in asymmetric epoxidations,[1] direct incorporation of tartaric acid's carbon framework into synthetic targets is also of interest. In previous communications we and others reported that appropriately functionalized forms of tartaric acid could serve as precursors to important derivatives of 3-hydroxy-4-alkoxycarbonyl-2-azetidinones **2**.[2,3] Since essentially any β-hydroxy acid can be converted to a β-lactam by the hydroxamate method,[4] the use of tartaric acid for β-lactam synthesis depended on the ability to differentiate its two carboxyl and hydroxyl groups, yet maintain its optical purity. French chemists accomplished the differentiation by separately incubating diethyl tartarates **3a,b** with pig liver esterase (PLE) to produce the corresponding half esters **4**.[3] Conversion to the corresponding hydroxamates **5** was followed by various attempts to form the β-lactams. Surprisingly, use of the usual Mitsunobu process[4,5] or mesylation followed by treatment with base produced only low yields of the β-lactams **6**. We had found that chemical differentiation of the carboxyl and hydroxyl groups of tartaric acid can be done efficiently.[2] Herein we report the details of this process and corrected structural assignments for some of the previously reported tartarate derivatives. The final results indicate that, under proper conditions, β-lactams can be formed nearly quantitatively from tartarate derived β-hydroxy-hydroxamates and in low yield from appropriately protected α-hydroxy-hydroxamates.

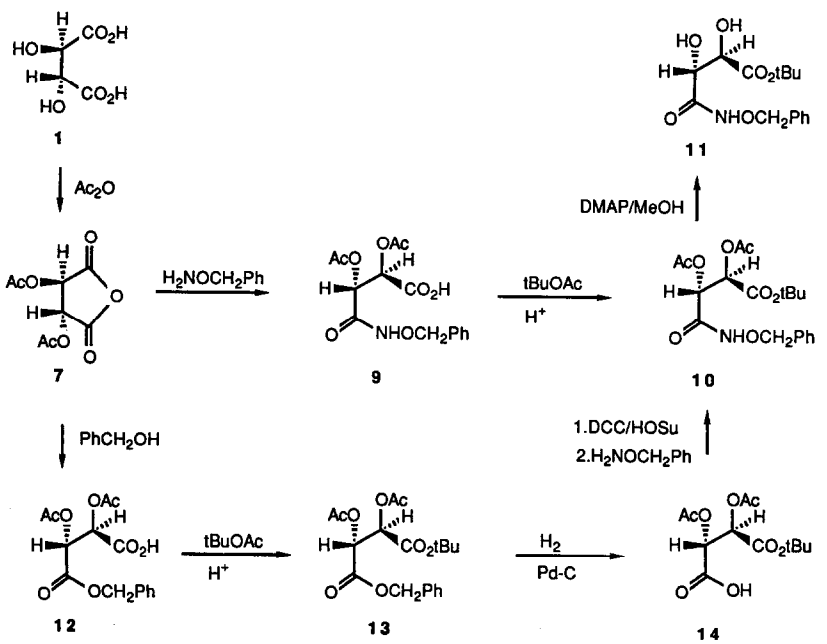
1 **2** eq 1

Scheme 1



The chemical differentiation of the symmetrically disposed functionality on tartaric acid was accomplished in a simple, but stepwise, manner. Diacetoxy succinic anhydride **7** was first prepared by treatment of L-(2R,3R)-(+)-tartaric acid (**1**) with acetic anhydride.[6] Reaction of the anhydride with O-benzylhydroxylamine(**8**) produced the hydroxamic acid **9**, thus differentiating the two carboxyl groups according to precedent.[6] The remaining carboxyl group was converted to the corresponding t-butyl ester by reaction with t-butyl acetate and perchloric acid.[7] The overall yield for the conversion of **7** to optically active **10** was 50% to 75% depending on whether the intermediates were isolated. A somewhat longer, but equally efficient process involved opening of anhydride **7** with benzyl alcohol to give monobenzyl tartarate **12**, conversion of the free carboxylic acid to the t-butyl ester **13** as before, and hydrogenation of the benzyl ester to produce the mono acid ester **14**. Formation of the N-hydroxysuccinimide ester of **14** followed by coupling with O-benzylhydroxylamine produced the carboxyl differentiated substrate **10**.

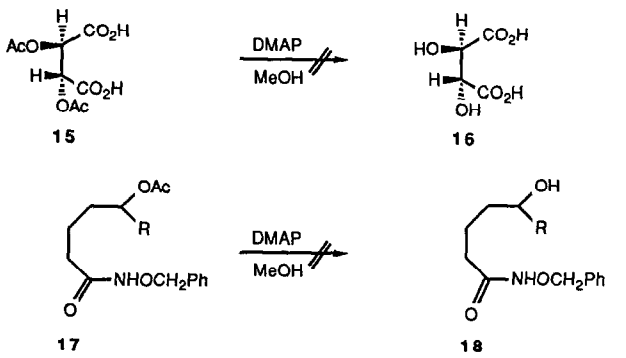
Scheme 2



Methanolysis of **10** in the presence of dimethylaminopyridine (DMAP) as a catalyst

produced the diol **11** quantitatively. This reaction with methanol and DMAP seems to be especially facile for α- and β-acetoxy- hydroxamates. The acetyl groups of diacetoxy succinic acid (**15**) were not removed even after 60 hr of reflux under the same conditions (Scheme 3). During the conversion of **10** to **11**, initial intramolecular transacetylation to the hydroxamate is suspected since δ-acetoxy hydroxamates **17** are inert to the same reaction conditions. In any event, successful application of tartaric acid derivatives to the synthesis of β-lactams now required differentiation of the two hydroxyl groups. After considerable study, we found that careful treatment of **11** with 100 mole percent of t-butyldimethylsilylchloride and 100 mole percent of imidazole resulted in clean formation of a single monosilyl tartarate derivative (**19a** or **19b**). Either treatment of this product with another 100 mole percent of imidazole or repetition of the initial silylation reaction with 200 mole percent of imidazole produced the other monosilyl tartarate exclusively. Although the silylation reactions readily distinguished between the two hydroxyl groups of the tartarates, the problem of assigning the correct structure to the isomers remained.

Sheme 3

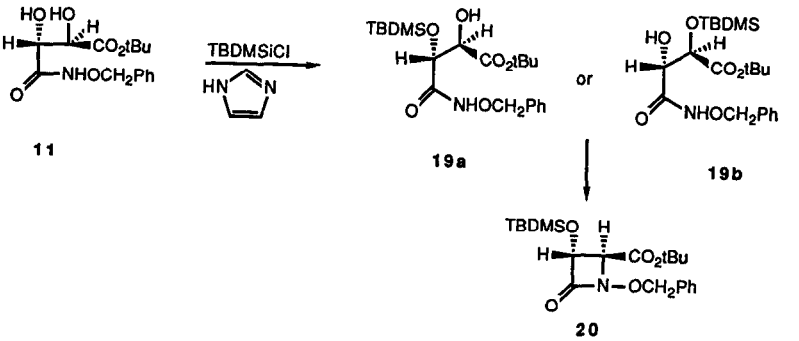


15 **16**

17 **18**

Direct structural assignment for the two isomers by spectroscopy was difficult. A 0.1 ppm difference (δ 3.36 to 3.46) in the chemical shift of one of the key methine protons was the primary difference in the ^{1}HNMR spectra of **19a** and **19b**. Based on comparisons with other tartarate derivatives we had prepared, we tentatively assigned the isomer with the methine resonance at δ 3.36 to the desired free β-hydroxy-hydroxamate **19a**. This structural assignment was apparently confirmed by treatment of this isomer with dimethyl azodicarboxylate and triphenylphosphine to produce the expected β-lactam **20**.[2] However, in contrast to most of our other β-hydroxy-hydroxamate cyclizations,[4] the yield was only 40% and actually lower when other azodicarboxylates were used. Still this yield was comparable to that obtained when the French workers attempted cyclization of their tartarate derived β-hydroxy-hydroxamates (**5** → **6**, 20-30%).[3] The overall conversion of our hydroxy-hydroxamate (**19a** or **19b**) to the β-lactam **20** was slightly improved by first preparation of the corresponding mesylate followed by treatment with base (KOH or K_2CO_3) in a benzene / DMSO mixture. The alternative use of the tosylate, which worked well for the French chemists,[3] resulted in production of only a 20% yield of the β-lactam. Even though our substrate contained a more bulky t-butyl rather than ethyl ester, this last result was the only real discrepancy that began to suggest problems with our structural assignment.

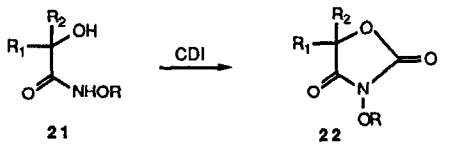
Scheme 4



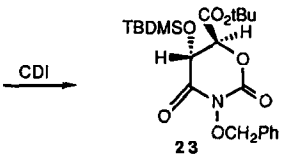
Despite the ability to prepare the β-lactams as described above, we have subsequently determined that our initial assignments[2] of the structures for the silyltartarates **19a,b** should be reversed. That is, reaction of **11** with 100 mole percent of t-butyldimethysilyl-chloride and 100 mole percent of imidazole produces the desired α-silyloxy-β-hydroxy hydroxamate **19a**, while use of 200 mole percent of imidazole produces the α-hydroxy-β-silyloxy hydroxamate **19b**. This conclusion is supported by further derivatization of the two isomers and successful conversion of the correct β-hydroxy-hydroxamate to the β-lactam in essentially quantitative yield.

The derivatization experiments were based on precedent established by Geffken.[8] He reported that reaction of α-hydroxy-hydroxamates **21** with carbonyldiimidazole (CDI) produced the expected five-membered ring heterocycles **22** (Scheme 5) which have a very characteristic high carbonyl stretching frequency (ca. 1830 cm^{-1}). Indeed, separate reactions of our tartarate derived hydroxy-hydroxamates (**19a** and **19b**) with CDI produced cyclic isomers (**23** and **24**) which were clearly distinguishable. The smaller, five-membered ring product **24** had carbonyl stretching frequencies of 1825, 1760, and 1725 cm^{-1} while those for the six-membered ring **23** were 1790, 1760, and 1720 cm^{-1}. In order to confirm that products of reactions of α-hydroxy-hydroxamates with CDI consistently display high frequency carbonyl stretches, we prepared a number of other α-hydroxy-hydroxamates **28a-c** in unambiguous fashion from amino acids **25a-c** and treated them with CDI. In all cases, the carbonyls of the resulting five-membered rings absorbed at 1830 and 1760 cm^{-1}. A β-hydroxy-hydroxamate **30** was also prepared unambiguously from malic acid[9] and treated with CDI to give the expected six-membered ring product **31** with IR absorbances at 1790, 1760 and 1720 cm^{-1}. Even the corresponding hydroxy mesyloxy and tosyloxy hydroxamates (**32a,b** and **35**) underwent cyclization with CDI, but a concomitant or subsequent elimination in each case produced the dehydrated products **34** (IR 1790, 1720 and 1680 cm^{-1}) and **35** (IR 1840, 1760 and 1720), respectively.

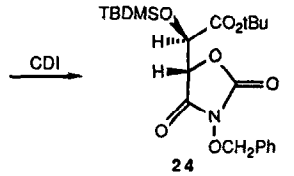
Scheme 5



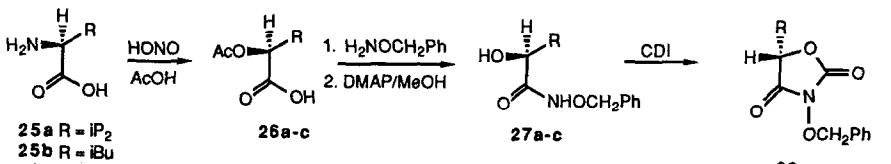
21 22



23

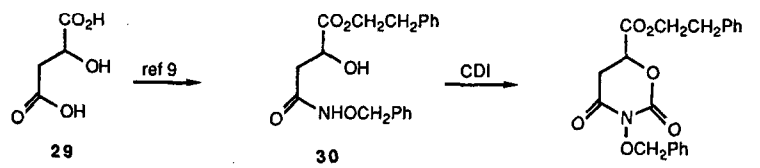


24



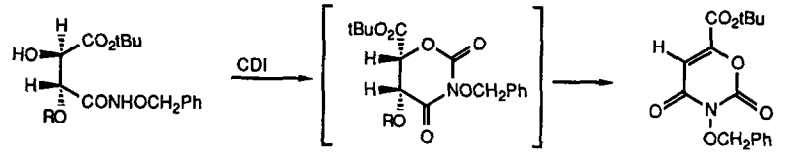
25a R = iP2
25b R = iBu
25c R = CH2Ph

26a-c 27a-c 28a-c



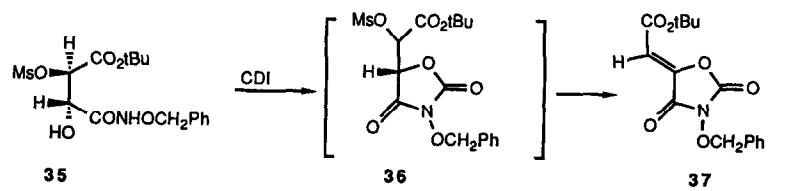
29 30 31

Scheme 6



32a R = Ms
32b R = Ts

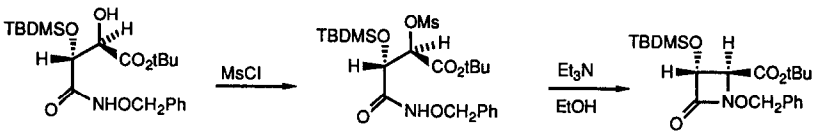
33a,b 34



35 36 37

With this correction and confirmation of our structural assignments of the important hydroxy-hydroxamates **19a** and **19b** completed, we studied the cyclization of the affirmed free β-hydroxy-hydroxamate **19a** to the corresponding β-lactam **20**. Variations of the Mitsunobu reaction in THF still were not efficient for the conversion of **19a** to the β-lactam. However, we found that the corresponding mesylate **38** could be quantitatively converted to the β-lactam by reaction with triethylamine in ethanol. The polar, protic solvent seems to greatly facilitate the cyclization and no problems associated with steric conjestion of the t-butyl ester was evident. Thus, using the correct β-hydroxy-hydroxamate isomer the overall conversion of tartaric acid to β-lactam **20** is extremely efficient. This highly functionalized β-lactam should be a useful synthetic precursor of a number of biologically interesting optically active monocyclic and bicyclic β-lactam antibiotics.

Scheme 7



19a **38** **20**

The only remaining question was how any β-lactam could have been previously obtained from cyclizations of what were now known to be the α-hydroxy-hydroxamates. While the mechanism for this unusual reaction has not yet been elucidated, several possibilities are being considered. Since silyl transfer from one oxygen to another (scrambling) has considerable precedent,[10] a similar process (**19b** to **19a**) during the Mitsunobu reactions might seem most reasonable. However, especially for the mesylates, alternative molecular rearrangements, including those which might proceed through intermediate, unstable aziridinones cannot yet be ruled out. Studies of these unusual reactions deserve further consideration.

Experimental Section

General Methods. Melting points were taken on a Thomas-Hoover Capillary Melting Point Apparatus and are uncorrected. Infrared spectra (IR) were recorded on a Perkin-Elmer 1420 Spectrophotometer. Proton NMR spectra were obtained on Varian EM-390, Magnachem A-200, or Nicolet NB-300 spectrometers. Chemical shifts are reported in ppm relative to tetramethylsilane (δ-units). Mass spectra were recorded on DuPont DP102 and Finnigan MAT Model 8430 spectrometers. Optical rotations were determined with a Rudolph Autopol III instrument. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ. All solvents were distilled and dried by standard methods.

O-Benzyl diacetoxysuccinohydroxamate 9. To 21.6 g (0.1 mole) of diacetoxysuccinic anhydride (**7**)[6] in 100 ml of anhydrous THF at 0°C was added, with stirring, 15 g (0.12 mole) of O-benzylhydroxylamine (**8**). The reaction was allowed to warm to room temperature and stirred overnight. The THF was then evaporated under reduced pressure. The residue was dissolved in a 5% $NaHCO_3$ solution and the excess O-benzylhydroxylamine was removed by extraction with several portions of ether. The water layer was acidified to pH 3 and the solution was extracted with several portions of ethyl acetate. The combined ethyl acetate extracts were washed with a saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated to provide 25.4 g (78%) of product (**9**) which was used directly in the next reaction.

4-t-Butyl O-benzyl diacetoxysuccinohydroxamate 10. Method A. A solution of 20.34 g (60 mmol) of **9** and 0.5 ml of 70% $HClO_4$ in 60 ml of t-butyl acetate was stirred overnight at room

temperature. The reaction mixture was slowly added portion-wise to 100 ml of saturated $NaHCO_3$. The resulting solution was extracted with several portions of ethyl acetate. The combined extracts were washed with a saturated solution of NaCl, dried over $MgSO_4$, filtered and evaporated to give 13g (55%) of the desired t-butyl ester **9** as an oil. ^{1}HNMR ($CDCl_3$, 90 MHz) δ 1.43 (s 9H), 2.07 (two s, 6 H), 4.9 (s, 2H), 5.53 (m, 1H), 5.84 (d, 1H, J = 3 Hz), 7.42 (s, 5H), 9.33 (br. s, 1H); mass spec (CI with isobutane) m/e: 396 (M+1), 340 (M-55); IR (film): 3200, 1730, 1670 cm^{-1}; $[\alpha]_D$ = +8.5 (c=1.7, CH_2Cl_2).

Method B. To a solution of 5.8 g (20 mmol) of **14** and 2.3 g (20 mmol) of N-hydroxy succinimide in 80 ml of ethyl acetate was added 4.12 g (20 mmol) of DCC in 20 ml of ethyl acetate at 0°C. The mixture was allowed to warm to room temperature and stirred for 4 h. The dicyclohexylurea was removed by filtration and the filtrate was concentrated to 50 ml. This concentrate was added to a solution of 5g (30 mmol) of O-benzylhydroxylamine hydrochloride and 3.36 g (40 mmol) of $NaHCO_3$ in water. The reaction mixture was stirred overnight. The mixture was transferred to a separatory funnel and extracted with water, 5% citric acid, water and brine. The organic layer was then dried over $MgSO_4$, filtered and evaporated to provide 7.5 g (97%) of pure product. The physical and spectral properties were identical to those obtained for the sample prepared by Method A, except for the optical rotation $[\alpha]_D$ = +8.0 (c = 4.5, CH_2Cl_2).

Benzyl diacetoxysuccinic acid 12. Diacetoxysuccinic anhydride (**7**) was first prepared from L-tartaric acid in 85% yield by the reported procedure.[6] ^{1}HNMR ($CDCl_3$, 90 MHz) δ 2.6 (s, 6H), 5.66 (s, 2H); IR (thin film) 1900, 1820, 1750 cm^{-1}. A catalytic amount (50 mg) of dimethylaminopyridine (DMAP) was added to 21.6g (0.1 mole) of **7** in 0.2 mole of benzyl alcohol and the reaction mixture was stirred overnight at room temperature. A 10% solution (100 ml) of $NaHCO_3$ was added and unreacted benzyl alcohol was extracted with several portions of ether. The aqueous layer was acidified to pH 3 by addition of 2N HCl and extracted with several portions of ethyl acetate. These latter ethyl acetate extracts were combined, washed with saturated NaCl, dried over $MgSO_4$, filtered and evaporated to provide 32 g (96%) of **12** as an oil. ^{1}HNMR ($CDCl_3$, 90 MHz) δ 1.87 (s, 3H), 2.1 (s, 3H) 5.2 (two d, 2H, J = 12 Hz), 5.75 (s, 2H), 7.35 (s, 5H), 9.2 (s, 1H); IR (film) 1740 cm^{-1} (broad); mass spec (CI with isobutane) m/e 325 (M+1), 324 (M^+), 264 (M-61), 240 (M-85), 217 (M-108); $[\alpha]_D$ = +28.5 (c = 0.8, CH_2Cl_2).

1-Benzyl 4-t-butyl diacetoxysuccinate 13. To 31.5 g (97.5 mmol) of **12** was added 100 ml of t-butyl acetate and a few drops of 70% perchloric acid. The reaction flask was sealed and allowed to stand 24 h at room temperature. The reaction mixture was slowly poured portion-wise into 200 ml of a saturated solution of $NaHCO_3$. The resulting mixture was extracted with several portions of ethyl acetate. The combined ethyl acetate layers were washed with a saturated solution of NaCl, dried over $MgSO_4$, filtered and evaporated. The residue was purified by silica gel chromatography eluting with hexanes - ethyl acetate (4:1) to give 23 g (62% yield) of **13**. ^{1}HNMR ($CDCl_3$, 90 MHz) δ 1.42 (s, 9H), 1.94 (s, 3H), 2.17 (s, 3H), 5.2 (two d, 2H, J = 12 Hz), 5.61 (d, 1H, J = 3 Hz), 5.77 (d, 1H, J = 3 Hz), 7.4 (s, 5H); IR (film) 1760 cm^{-1}; mass spec (CI with isobutane) m/e 381 (M+1), 324 (M-56); $[\alpha]_D$ = +33.3 (c=1.2, CH_2Cl_2).

It should be noted that the overall yield of **13** was substantially increased when the synthesis was performed on a large scale without isolation of intermediates. Thus, 270 g (70%) of **13** along with 70 g (22%) of **12** was obtained from 150 g (1 mole) of L-tartaric acid.

Mono t-butyl diacetoxysuccinate 14. The diester **13** (7.6 g (20 mmol) was dissolved in ethyl acetate and hydrogenated at one atmosphere of H_2 over 10% Pd-C to provide 5.8 g (100%) of **14** as an oil. ^{1}HNMR ($CDCl_3$, 90 MHz) δ 1.45 (s, 9H), 2.16 (s, 6H), 5.62 (d, 1H, J = 3 Hz), 5.75 (d, 1H, J = 3Hz), 6.53 (s, CO_2H); IR (film) 3500 - 2500 (br), 1735, 1715 cm^{-1}; mass spec (CI with isobutane) m/e 291 (M+1), 235 (M-56), 217 (M-73); $[\alpha]_D$ = +0.7 (c = 3.5, MeOH), +4.1

(c = 1.4, acetone).

O-Benzyl 4-t-butyl (L)-tartarohydroxamate 11. A solution of 15.8 g (40 mmol) of **10** and 490 mg (4 mmol) of DMAP in 200 ml of MeOH was heated at reflux for 1.5 h after which TLC analysis showed complete disappearance of the starting diacetate. The methanol was evaporated and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 10% citric acid in water, water, brine, dried over $MgSO_4$, filtered and evaporated. Recrystallization (carbon tetrachloride) provided 10.5 g (84% yield) of **11.** Mp 116 - 117°C; ^{1}HNMR ($CDCl_3$, 90 MHz) δ 1.5 (s, 9H), 3.53 (m, 1H), 3.95 (m, 1H), 4.52 (m, 2H), 4.9 (s, 2H), 7.4 (s, 5H), 9.5 (br. s, 1H); IR (nujol) 3500, 3390, 3275, 1725, 1670 cm^{-1}; mass spec (CI with isobutane) m/e 312 (M+1); $[\alpha]_D$ = +28.3 (c = 1.9, THF, for the material made using the sequence that starting with **12**) and +28.5 (c = 2, THF for the material made using the sequence starting with **9**). Analysis, calcd for $C_{15}H_{21}NO_6$: C (57.88), H (6.75), N (4.50). Found: C (58.00), H (6.48), N (4.56).

O-Benzyl 3-(O-t-butyldimethylsilyl)-4-t-butyl-(L)-tartarohydroxamate 19a. To 1.244 g (4 mmol) of **11** in 20 ml of DMF was added 632 mg (4.1 mmol) of t-butyldimethylsilylchloride (TBDMSCl) and 280 mg (4.1 mmol) of imidazole and the reaction mixture was allowed to stand at room temperature for 24 h. The mixture was then poured into 100 ml of water and extracted with several portions of ethyl acetate. The combined ethyl acetate layers were washed with water and brine. The solution was then dried over $MgSO_4$, filtered, and evaporated. The residue was chromatographed on silica gel eluting with methylene chloride - methanol (5:1) to provide 1.6 g (94%) of **19a** and 40 mg (4%) of the starting material. The characterization data for **19a** includes: ^{1}HNMR ($CDCl_3$, 90 MHz) δ 0.77 (s, 9H), 1.46 (s, 9H), 3. 46 (d, 1H, J = 9 Hz), 4.24 (d, 0.5 H, J = 1.5 Hz), 4.36 (d, 0.5 H, J = 1.5 Hz), 4.5 (d, 1H, J = 1.5 Hz), 4.94 (s, 2H), 7.4 (m, 5 H), 8.87 (s, 1H); IR (thin film) 3390, 3290, 1730, 1695 cm^{-1}; mass spec (CI with isobutane) m/e 426 (M+1). $[\alpha]_D$ = + 51.2 (c = 0.95, CH_2Cl_2).

O-Benzyl 2-(O-t-butyldimethylsilyl)-4-t-butyl-(L)-tartarohydroxamate 19b. To a solution of 1.244 g (4 mmol) of **11** in 10 ml of dry DMF was added 632 mg (4.1 mmol) of TBDMSCl and 581 mg (8.1 mmol) of imidazole and the reaction mixture was stirred for 24 h. Water (100 ml) was added and the mixture was extracted with several portions of ethyl acetate. The combined ethyl acetate layers were washed with water, brine, dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel as described for **19a** to provide 1.4 g (82% yield) of **19b** as an oil along with 150 mg (12%) of the starting material. The characterization data for **19b** includes ^{1}HNMR ($CDCl_3$, 90 MHz) δ 0.87 (s, 9H), 1.43 (s, 9H), 3.36 (d, 1H, J = 7 Hz), 4.33 (m, 1H), 4.66 (d, 1H, J = 1.5 Hz), 4.9 (s 2H), 7.36 (s, 5H), 9.33 (s, 1H); IR (thin film) 3290 (with a shoulder at 3390), 1740 and 1670 cm^{-1}; mass spec (CI with isobutane) m/e 426 (M+1), 370 (M-56). $[\alpha]_D$ = +93.3 (c = 0.7, CH_2Cl_2).

Synthesis of O-benzyl α-hydroxy-hydroxamates. The corresponding α-amino acids were first transformed into α-acetoxy acids as previously described.[11] The α-acetoxy acids were converted to the O-benzyl hydroxamates by the same procedure used for the preparation of **10.** Methanolysis in the presence of DMAP as described for the preparation of **11** gave the desired products with the following characterization data.

27a: 70% yield, mp 60-62°C; ^{1}HNMR ($CDCl_3$, 90 MHz) δ 0.9 (two d, 6H, J = 7 Hz), 2.1 (m, 1H), 3.66 (br. s, 1H), 3.97 (t, 1H), 4.86 (s, 2H), 7.38 (s, 5H), 9.43 (br. s, 1H); IR (nujol) 3400, 3240, 1635 cm^{-1}; $[\alpha]_D$ = -11.6 (c = 3, CH_2Cl_2); Analysis, calcd for $C_{12}H_7NO_3$: C (64.57), H (7.62), N (6.28). Found: C (64.61), H (7.58), N (6.30).

27b: 77% yield, mp 65-67°C; ^{1}HNMR ($CDCl_3$, 90 MHz) δ 0.88 (d-d, 6H, J = 7 Hz and 3 Hz), 1.56 (m, 2H, J = 7 Hz), 1.76 (m, 1H, J = 7 Hz), 3.82 (br. s, 1H), 4.1 (t, 1H, J = 7 Hz), 4.72 (s, 2H), 7.33 (s, 5H), 9.43 (br. s, 1H); IR (nujol) 3500, 3220, 1640 cm^{-1}; $[\alpha]_D$ = -12.6 (c = 2.4, CH_2Cl_2); Analysis, calcd for $C_{13}H_{19}NO_3$: C (65.82), H (8.,02), N (5.91). Found: C (65.91), H (8.06), N (6.05).

27c: 51% yield, mp 125-126°C; ^{1}HNMR ($CDCl_3$, 90 MHz) δ 2.9 (two d, 2 H, J = 7 Hz), 4.27 (br. s, 1H), 4.53 (m, 1H, J = 7 Hz), 4.85 (s, 2H), 7.33 (s, 5H), 7.40 (s, 5H), 10.3 (br. s, 1H); IR (nujol) 3220, 1655 cm^{-1}; mass spec (Cl with isobutane) m/e 272 (M+1).

Reactions of hydroxy-hydroxamates with carbonyldiimidazole; general procedure. To a solution of 1 mmol of the O-benzyl α- or β-hydroxyhydroxamate in 10 ml of anhydrous CH_2Cl_2 was added 1.5 mmol of carbonyldiimidazole and the reaction mixture was stirred for 15 to 30 min at room temperature. The time was determined by monitoring each separate reaction by TLC. The solution was then concentrated under reduced pressure to about 5 ml. The residue was chromatographed on silica gel eluting with ethyl acetate - hexanes (1:3). Characterization data for the products includes the following.

23: 98% yield, oil; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.144 (s, 3H), 0.205 (s, 3H), 0.919 (s, 9H), 1.481 (s, 9H), 4.64 (d, 1H, J = 6 Hz), 4.71 (d, 1H, J = 6 Hz), 7.369 (m, 3H), 7.54 (m, 2H); IR (thin film) 1790, 1740 cm^{-1}; mass spec (Cl with isobutane) m/e 452 (M+1), 396 (M-56), 346.

24: 92% yield, mp 132-133°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.032 (s, 3H), 0.127 (s, 3H), 0.864 (s, 9H), 1.496 (s, 9H), 4.553 (d, 1H, J = 1.8 Hz), 5.104 (d, 1H, J = 1.8 Hz), 5.141 (s, 2H), 7.408 (m, 3H), 7.49 (m, 2H); IR (nujol) 1830, 1760, 1745 cm^{-1}; mass spec (Cl with isobutane) m/e 452 (M+1), 396 (M-56), 346, 290.

28a: 99% yield, oil; ^{1}HNMR ($CDCl_3$, 300 MHz), δ 0.86 (d, 3H, J = 7 Hz), 1.03 (d, 3H, J = 7 Hz), 2.2 (m, 1H), 4.54 (d, 1H, J = 4 Hz), 7.4 (m, 3H), 7.5 (m, 2H); IR (thin film) 1830, 1760 cm^{-1}; mass spec (Cl with isobutane) 250 (M+1).

28b: 99% yield, mp 82-84°C; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 0.95 (two d, 6H, J = 6 Hz), 1.54 (m, 1H), 1.7 (m, 1H), 1.85 (m, 1H), 4.7 (two d, 1H, J = 4 Hz), 7.4 (m, 3H) 7.5 (m, 2H); IR (nujol) 1820, 1760 cm^{-1}; mass spec (Cl with isobutane) m/e 264 (M+1), 220 (M-44).

28c: 99% yield, mp 129-130°C; ^{1}HNMR (in $CDCl_3$, 300 MHz) δ 3.1 (two d, 1H, J = 5 Hz), 3.3 (two d, 1H, J = 5 Hz), 4.7 (d-d, 2H, J = 10 Hz), 4.97 (d-d, 1H, J = 4.5 Hz), 7.23 (m, 5H), 7.3 (s, 5H); IR (nujol) 1825, 1760, 1735 cm^{-1}; mass spec (Cl with isobutane) m/e 298 (M+1), 264 (M-34).

31: 40% yield, oil; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 2.96 (t, 2H, J = 7 Hz), 3.1 (two d-d, 2H, J = 6 Hz, and 5 Hz), 4.42 (two t, 2H, J = 7 Hz and 6 Hz), 4.88 (dd, 1H, J = 6 Hz and 5 Hz), 4.98 (d, 2H, J = 2 Hz), 7.3 (m, 10H); IR (nujol) 1790, 1770, 1720 cm^{-1}; mass spec (Cl with isobutane) m/e 370 (M+1), 326 (M-44).

34: 61% yield starting with **32b** or 34% yield starting with **32a**, mp 123-124°C; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 1.52 (s, 9H), 5.13 (s, 2H), 6.65 (s, 1H), 7.4 (m, 3H), 7.53 (m, 2H); IR (nujol) 1790, 1720 cm^{-1}; mass spec (Cl with isobutane) m/e 320 (M+1).

37: 24% yield, mp 66-69°C; ^{1}HNMR ($CDCl_3$, 300 MHz) δ 1.5 and 1.52 (two s, ratio 1:6, 9H), 5.19(s, 2H), 6.05 and 6.12 (two s, ratio 1:6, 1H), 7.4 (m, 3H), 7.46 (m, 2H); IR (nujol) 1840, 1760, 1720, 1695 cm^{-1}; mass spec (Cl with isobutane) m/e 320 (M+1), 264 (M-56); Exact mass calcd for $C_{16}H_{17}NO_6$ 319.1056. Found: 319.1053.

O-Benzyl 2-(O-t-butyldimethylsilyl)-3-(O-methanesulfonyl)-4-t-butyl tartarohydroxamate 38. To 4 g (9.4 mmol) of **19a** in 20 ml of pyridine at 0°C was added slowly by syringe 0.74 ml (9.5 mmol) of methanesulfonyl chloride. The reaction was stirred for 4 h and then poured into ice water. The mixture was extracted with several portions of ether. The combined ether extracts were washed with 10% citric acid, water, a 5% $NaHCO_3$ solution and brine. The solution was then dried over $MgSO_4$, filtered and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate - hexanes (1:10) to provide 4.5 g (95%) of the product as an oil. ^{1}HNMR ($CDCl_3$, 90 MHz) δ 0.8 (s, 9H), 1.5 (s, 9H), 3.1 (s, 3H), 4.76 (d, 1H, J = 2 Hz), 5.0 (s, 2H), 5.2 (d, 1H, J = 2 Hz), 7.43 (s, 5H), 8.8 (s, 1H); IR (thin film) 3390, 1745, 1690 cm^{-1}; mass spec (CI with isobutane) m/e 504 (M+1) 448 (M-56), 390 (M-114); $[\alpha]_D$ = +78.5 (c = 1.2, CH_2Cl_2). Analysis, calcd for $C_{22}H_{37}NO_8SSi$: C (52.49), H (7.36), N (2.78). Found: C (52.35), H (7.08), N (2.85).

3-t-butyldimethylsilyloxy-4-t-butoxycarbonyl-2-azetidinone 20. To 210 mg (0.4 mmol) of **38** in 15 ml of ethanol was added 0.07 ml (0.5 mmol) of triethylamine and the reaction mixture was allowed to stir at room temperature for five days. The ethanol was then removed under reduced pressure and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed with 5% citric acid, water, brine and then dried over $MgSO_4$. Evaporation of the ethyl acetate in vacuo provided 162 mg (~ 100%) of product. Mp 44-45°C; ^{1}HNMR ($CDCl_3$, 90 MHz) δ 0.9 (s, 9 H), 1.5 (s, 9H), 3.86 (d, 1H, J = 1.5 Hz), 4.57 (d, 1H, J = 1.5 Hz), 5.1 (s, 2H), 7.42 (s, 5H); IR (thin film) 1795, 1740 cm^{-1}; mass spec (CI with isobutane) m/e 408 (M+1), 381 (M-57); $[\alpha]_D$ = +45 (c = 3.07, CH_2Cl_2).

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References and Notes

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