HETEROCYCLES, Vol. 55, No. 11, 2001, pp. 2099 - 2108, Received, 30th July, 2001

A FACILE ENTRY TO BICYCLIC SYSTEMS FROM L-GLUTAMIC ACID

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Abstract - An efficient synthesis of bicyclic heterocycles has been realized from L-glutamic acid. The key step is the construction of the pyrrole ring *in a single step*, using tosylmethyl isocyanide (TosMIC) methodology. Structures of reaction intermediates and final products were investigated using density functional theory calculations.

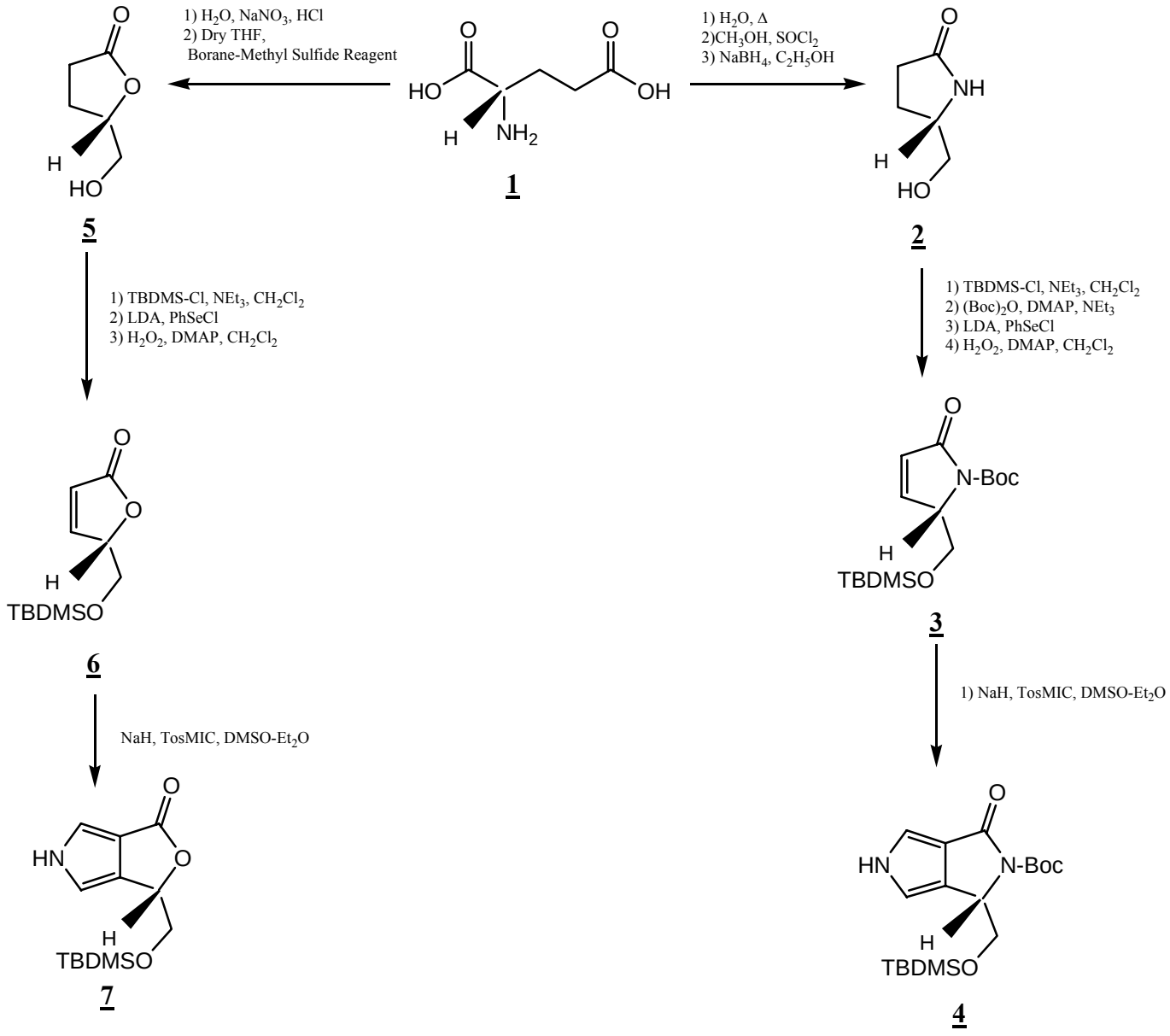
INTRODUCTION

Optically active α-amino aldehydes,[1] as well as the corresponding α-amino acids,[2] have potential as chiral building blocks for the synthesis of novel polyfunctional amino acids, amino polyols, and peptide mimics, that include enzyme inhibitors, aminosugar antibiotics, and sympathomimetic amines. For example, the use of amino acids as synthons for various heterocyclic systems, including pyrroles, has been documented.[3] Recently, a titanium mediated cyclization reaction has been reported that provides an efficient and practical method for synthesizing *N*-heterocycles from amino acids.[4] In spite of the fact that numerous synthetic routes exist for the preparation of this important class of heterocyclic compounds, many of these procedures provide limited access in terms of substituents and substitution patterns.[5] Thus the development of new methodologies for the synthesis of substituted pyrroles is an area of continued interest.

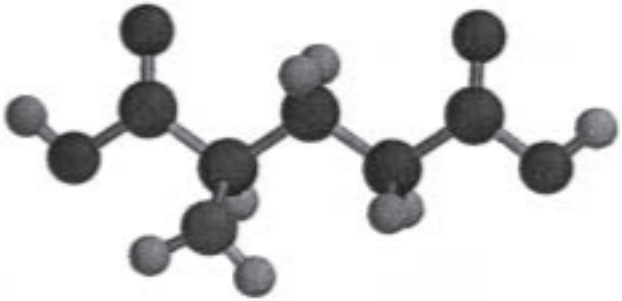
L-Glutamic acid (**1**) is a naturally occurring, inexpensive amino acid and is a well-known substrate from the chiral pool. The synthetic pathway described here utilizes construction of a pyrrole ring system, *in a single step*, using TosMIC methodology. This procedure provides an easy entry to bicyclic substituted pyrroles and their oxygen analogs from readily available chiral starting material *via* conventional transformations of functional groups.

RESULTS AND DISCUSSION

L-Glutamic acid (**1**) was first converted to the lactam (**2**) and then to the α,β-unsaturated protected lactam (**3**) following literature procedures[6,7] with minor modifications as described in EXPERIMENTAL. All the reagents used in the synthetic sequence are inexpensive, non-hazardous and the resulting products are obtained in pure form without any chromatographic purification. All reaction products in the intermediate steps were characterized by spectral data (IR and NMR). The structures of **1**, **2** and **3** were investigated using density functional theory (DFT) at the BP/DN** computational level, as implemented in Spartan 5.0.[8] In each case several different conformers were optimized. The lowest-energy structures of **1-3** we found are shown in Figure 1.



The second step in the synthetic sequence involves the construction of the pyrrole ring system using the procedure developed by Van Leusen *et al*.[9] and subsequently employed by us[10] and others.[11] This general



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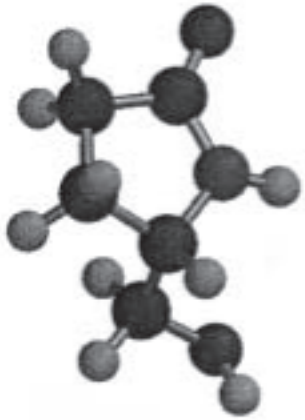

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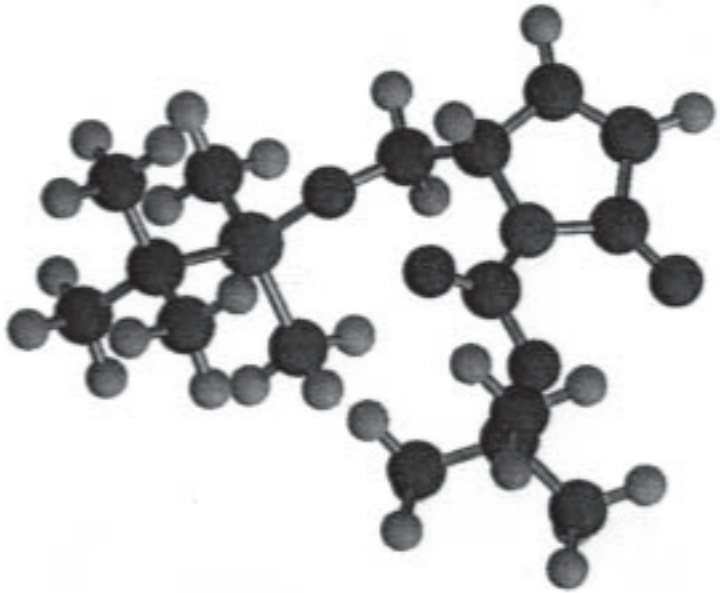

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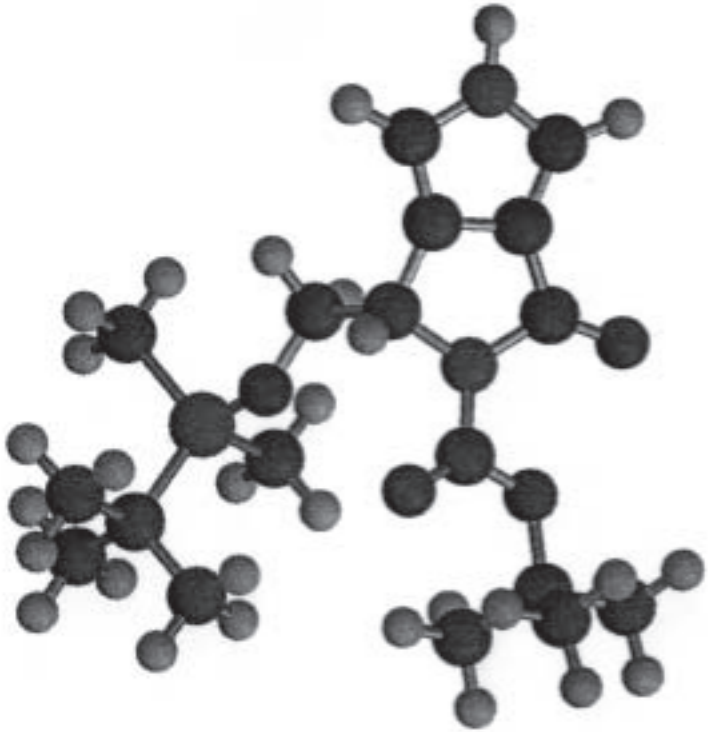

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Figure 1

route to substituted pyrroles involves conjugate addition of isocyanide-derived carbanions stabilized by an additional electron withdrawing group to a variety of α,β-unsaturated functional groups, e.g. ester, ketone, nitro and sulfone. Substituted TosMIC reagents have also found synthetic uses.[12] Reaction of **3** with 3.6 equivalents of sodium hydride and 3 equivalents of TosMIC generated the bicyclic derivative (**4**) in 97.8% yield. The BP/DN** optimized structure is shown in Figure 1.

For the synthesis of the oxygen analog, L-glutamic acid was first converted to γ-butyrolactone (**5**).[13] The hydroxyl group was then protected and the resulting silyl derivative was subjected to selenylation-deselenylation using conditions we developed during the course of this study for the lactam (**2**) to afford the α, β-unsaturated lactone (**6**) in 61% yield for the three step sequence. Treatment of **6** with 1.2 equivalents of NaH and 1 equivalent of TosMIC gave the bicyclic derivative (**7**) in 87% yield. The corresponding structures are shown in Figure 2.

EXPERIMENTAL

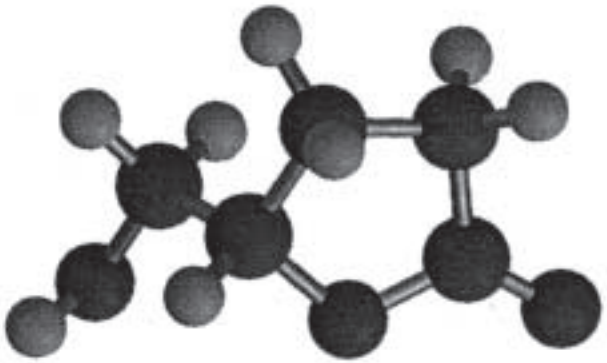
General Methods

All reactions were carried out under a nitrogen atmosphere. Glassware was oven dried and cooled to rt under a nitrogen atmosphere. Ether was distilled from sodium benzophenone ketyl. DMF and DMSO were distilled under reduced pressure and stroed over 4Å molecular sieves. The melting points reported are uncorrected. ^{1}H NMR spectra were measured at 60 and 500 MHz using acetone-d_6 as solvent. TLC was performed on 0.25 mm precoated silica plates (60F-254); the plates were initially examined under UV light and spots were then visualized with iodine and a 7% solution of phospomolybdic acid in ethanol. Silica gel (70-230 mesh) was used for column chromatography. Optical rotations were recorded on a Perkin-Elmer Model 241 Polarimeter.

Computational Methods

All optimizations were performed using the highly efficient Becke-Perdew (BP) density functional with the numerical DN** basis set, as implemented in Spartan 5.0.[8] This non local (gradient corrected) BP/DN** method[14] incorporates the effects of electron correlation into the optimization and the DN** basis set includes *d*-type polarization functions on all the heavy atoms and *p*-type polarization functions on all the hydrogen atoms. No symmetry constraints were employed during the optimizations.

(+)-(2*S*)-2-Hydroxymethyl-5-pyrrolidinone (2)- L-Glutamic acid (25 g, 194 mmol) was refluxed in water (125 mL) for 48 h. The solvent was evaporated and the residue was azeotropically dried with methanol. The resulting thick viscous liquid was suspended in dry methanol (100 mL) and freshly



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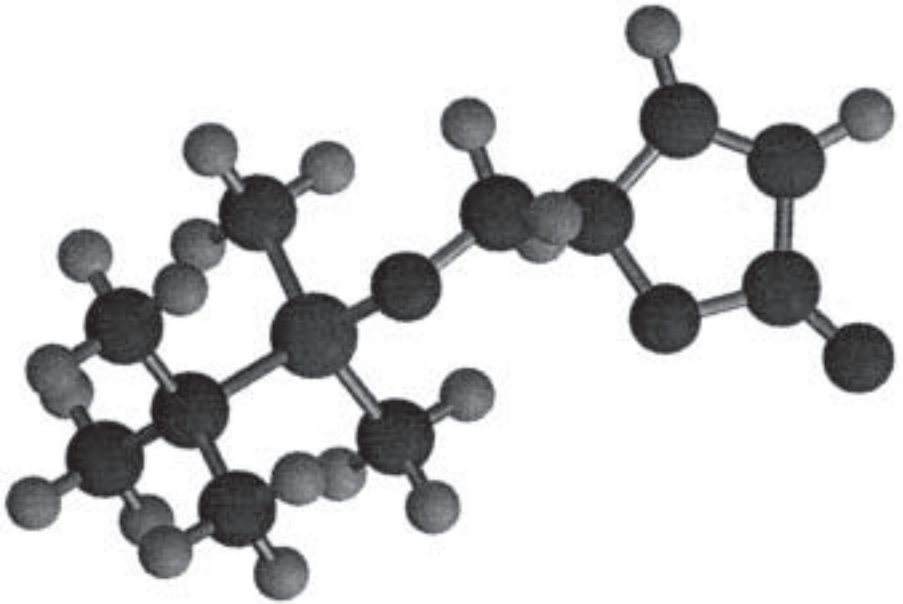

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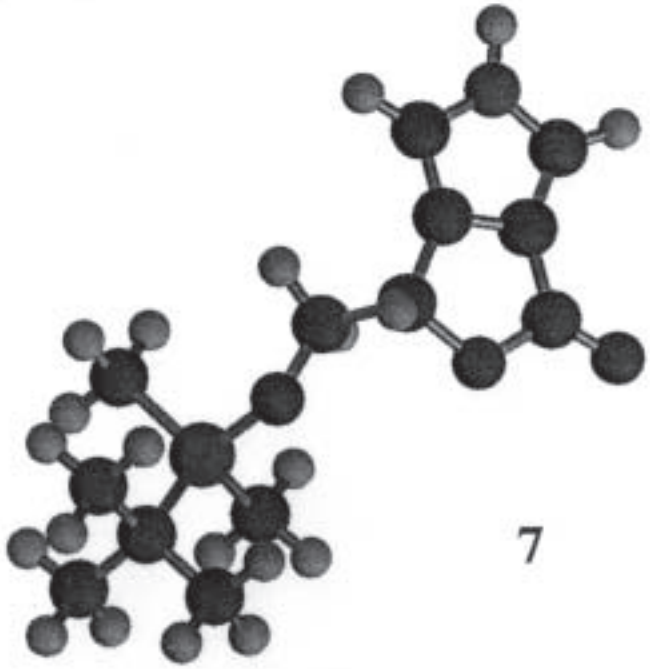

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Figure 2

distilled thionyl chloride (2 mL) was added and the solution was stirred for 48 h at rt. Sodium bicarbonate was then added until the mixture was of a neutral pH and then the solvent was rotary evaporated. The residue was extracted with ethyl acetate (100 mL) and washed with water (20 mL). The organic layer was dried over sodium sulfate and evaporated to afford (+)-methyl (2*S*)-5-oxopyrrolidine-2-carboxylate (27.48 g, 90.1%). A portion of this ester (5.89 g, 37.5 mmol) was dissolved in dry ethanol (236 mL) and sodium borohydride (2.59 g, 68.5 mmol) was added. The reaction mixture was stirred for 3 h at rt. Acetone (11.8 mL) was added to the solution and allowed to stir for an additional 30 min. The reaction mixture was acidified using conc. hydrochloric acid (4.2 mL) to pH 4.0 The residue was extracted with ethyl acetate (100 mL) and washed with water (15 mL). The organic layer was dried over sodium sulfate and evaporated to yield **2** (4.012 g, 82.9 %) as a viscous liquid.

(5*S*)-*N*-(*tert*-Butoxycarbonyl)-5-(((*tert*-butyldimethylsilyl)oxy)methyl)-3-pyrrolin-2-one (3)
Compound (**2**) (2.0 g, 17.4 mmol) was dissolved in acetone (15 mL) by gentle warming. To this solution, dry dichloromethane (30 mL), *tert*-butyldimethylsilyl chloride (3.142 g, 20.8 mmol), and triethylamine (5.924 mL, 43.4 mmol) were added and the reaction mixture was stirred for 12 h at rt. The solvent was evaporated and the residue was extracted with ethyl acetate (100 mL) and washed with water (20 mL). The organic layer was dried over sodium sulfate and evaporated to yield yellowish crystals (1.750 g, 7.6 mmol). This solid was dissolved in THF (30 mL) and then cooled to 0°C. Triethylamine (2.13 mL, 15.3 mmol), 4-dimethylaminopyridine (1.025 g, 8.4 mmol), and di-*tert*-butyl dicarbonate (1.832 g, 8.4 mmol) were added to the mixture at 0°C and then stirred overnight at rt. The reaction was quenched with 5% aqueous citric acid (15 mL); the organic layer was dried over sodium sulfate and the solvent was evaporated to give solid yellowish crystals (2.41g; 7.3 mmol); $[\alpha]_D^{23}$ –60° (c 1.0, $CHCl_3$) (lit.,[15] $[\alpha]_D^{25}$ – 61° (c 1.1, $CHCl_3$)).

A solution of this compound (1.6 g, 4.85 mmol) in dry THF (5 mL) was added drop by drop to a solution of LDA [prepared from iPr_2NH (2.38 mL, 17 mmol) and *n*-BuLi (2.5 M in hexane solution, 0.54 mL, 5.87 mmol) at -78°C under nitrogen. The solution was stirred for 30 min at -78°C. Then a solution of phenylselenenyl chloride (1.125 g, 5.87 mmol) in dry THF (5 mL) was added and the reaction mixture was stirred for an additional 30 min. It was then quenched with 5% aqueous ammonium chloride (5 mL), allowed to warm to rt and extracted with ethyl acetate. The organic layer was dried over sodium sulfate and concentrated to yield the phenylselenyl compound as an orange colored solid (0.778 g, 1.6 mmol). The product, without any purification, was dissolved in dichloromethane (15 mL) and 30% hydrogen peroxide (3 mL, 126.98 mmol), and 4-dimethylaminopyridine (0.787 g, 6.44 mmol) were added. The reaction mixture was allowed to stir overnight. The reaction was quenched using 5% hydrochloric acid

(10 mL) and an additional amount of dichloromethane (10 mL) was used to extract the product. The organic layer was dried over sodium sulfate and then concentrated to yield **3** (1.391 g, 86.9%). An analytical sample was obtained by column chromatography on silica gel using ether; hexane (1:4) as eluant, mp 92-94°C. (lit.,[7] mp 64-65˚C); $[\alpha]_D^{23}$ –170.2° (c 1.0, $CHCl_3$) (lit.,[7] $[\alpha]_D^{25}$ –175.6° (c 0.9, $CHCl_3$)); IR and NMR spectra identical to the reported values.[7]

Reaction of Compound (3) with TosMIC

Pentane (5 mL) was added to sodium hydride (60% mineral oil, 0.220 g, 5.50 mmol). After stirring for 5 min the pentane was decanted off. To the dry sodium hydride under a nitrogen atmosphere was added TosMIC (0.895 g, 4.58 mmol) in dry ether (5 mL) and DMSO (2.5 mL). Compound (**3)** (0.500 g, 1.53 mmol) was then added to the mixture in dry ether (5 mL) and DMSO (2.5 mL) over a period of 10 min. The mixture was stirred at rt for 2 h. The residue was extracted with ether (20 mL) and washed with water (20 mL). The organic layer was dried over sodium sulfate and evaporated to yield **4**, (0.548 g, 97.8 %) as colorless crystals; mp 90°C. An analytical sample was prepared by passing through a short path of silica gel using hexane-ethyl acetate (7:3) as eluant. NMR δ 0.08-0.10 (6H, m), 1.00-1.10 (9H, m), 1.52 (9H, s), 3.70 (1H, m), 4.30 (2H, m), 6.50 (1H, m), 7.20 (2H, m). Anal. Calcd for $C_{18}H_{30}N_2O_4Si$: C, 58.98; H, 8.25; N, 7.64. Found: C, 58.88; H, 8.29; N, 7.60; $[\alpha]_D^{23}$ – 20.6° (c 0.9, $CHCl_3$).

(S)–(+)-γ-Hydroxymethyl-γ-butyrolactone (5)

A solution of sodium nitrite (7 g, 100 mmol) in water (15 mL) was added dropwise to a mixture of L-glutamic acid (10 g, 68 mmol) in water (26.67 mL) and conc. hydrochloric acid (14 mL) at 0-5˚C under vigorous stirring (6 h). The clear solution was stirred at rt overnight. The solvent was rotary evaporated and then extracted with ethyl acetate (33 mL). The insoluble material was filtered by suction and the organic solution was dried over sodium sulfate. Evaporation of the solvent affored s(+)-γ-carboxy-γ-butyrolactone as thick viscous oil (4.334 g, 49%). This product without purification was dissolved in dry THF (30 mL) and under nitrogen atmosphere borane-methyl sulfide reagent (3.81 mL, 38.1 mmol) was added slowly (50 min). The reaction mixture was stirred for 3 h and cautiously quenched with dry methanol (2.7 mL). Evaporation of solvent afforded **5** as thick liquid (4.20 g, 53.1%). An analytical sample was obtained by purification on silica gel column using chloroform: ethanol (90:10) as eluant. NMR δ 2.00-2.80 (4H, m); 3.60-4.00 (3H, m); 4.65 (1H, m); $[\alpha]_D^{20}$ +30.1° (c 0.4, EtOH) (lit.,[13] $[\alpha]_D^{26}$ +31.3° (c 2.92, EtOH)).

5-0-(*tert*-butyldimethylsilyl)-2, 3-dideoxy-L-glyceropentonic Acid γ-Lactone (6)

A mixture of **5** (4.20 g, 36.1 mmol), dry dichloromethane (50 mL), *tert*-butyldimethylsilyl chloride (6.537 g, 43.32 mmol), and triethylamine (12.59 mL, 90.25 mmol) were stirred at rt for 12 h. Solvent was evaporated and the residue was extracted with ethyl acetate (100 mL) and washed with water (20 mL). The organic layer was dried over sodium sulfate and evaporated to yield the corresponding silyl derivative (7.863 g, 94.5%). A solution of this compound in dry THF (15 mL) was added to a solution of LDA [prepared from iPr_2NH (5.26 mL, 37.51 mmol) and *n*-BuLi (1.6 M in Hexane solution, 21.35 mL] at -78˚C. Then a solution of phenylselenium chloride (7.837 g, 40.92 mmol) in dry THF (15 mL) was added and the reaction mixture was stirred for an additional 30 min. The reaction mixture was quenched with 5% ammonium chloride (15 mL) and allowed to warm to rt. The mixture was then extracted with THF (30 mL) and the organic layer was dried over sodium sulfate, concentrated to yield the phenylselenyl compound (10.157 g, 26.3 mmol). This product without any purification was dissolved in dry dichloromethane (30 mL) and 30% hydrogen peroxide (7.77 mL, 262.8 mmol), and 4-dimethylaminopyridine (12.843 g, 105.12 mmol) were added. The reaction mixture was allowed to stir overnight. It was then quenched with 5% hydrochloric acid (20 mL) and an additional amount of dichloromethane (20 mL) was used to extract the product. The organic layer was dried over sodium sulfate and then concentrated. Recrystallization of the crude product using methanol gave **6** (5.021 g, 84%), mp 87-88˚C. IR 3027, 2925, 1601, 1492, 1452, 901; NMR δ 0.04 (6H, s), 0.90 (9H, s), 4.20 (2H, m), 4.50 (1H, m), 6.50 (1H, m), 7.00 (1H, m). Anal. Calcd for $C_{11}H_{20}O_3Si$: C, 57.86; H, 8.83. Found: C, 57.78; H, 8.78; $[\alpha]_D^{23}$ – 73.5° (c 2.3, CH_3OH).

Reaction of Compound (6) with TosMIC

Pentane (5 mL) was added to sodium hydride (60% mineral oil, 0.0525 g, 2.63 mmol). After stirring for 5 min at 0˚C, the pentane was decanted off. To the dry sodium hydride under a nitrogen atmosphere was added TosMIC (0.427 g, 2.19 mmol) in dry ether (5 mL) and DMSO (2.5 mL). Compound (**6**) (0.500 g, 2.19 mmol) was then added to the mixture in dry ether (5 mL) and DMSO (2.5 mL) over a period of 10 min. The mixture was stirred at rt for 2 h. The residue was extracted with ether (20 mL) and washed with water (20 mL). The organic layer was dried over sodium sulfate and evaporated to yield **7** as colorless crystals. An analytical sample was prepared by passing through a short path of silica gel using a 3:1 ethyl acetate:hexane as eluant; mp 89-90˚C [solvent of recrystallization (ethylacetate:hexane)]. NMR δ 0.30 (6H, m), 0.90 (9H, s), 3.80 (3H, m), 7.00 (1H, brs), 7.80 (1H, m), 8.20 (1H, m). Anal. Calcd for $C_{13}H_{21}NO_3Si$: C, 58.33; H, 7.91; N 5.23. Found: C, 58.42; H, 7.97; N, 5.33; $[\alpha]_D^{23}$ – 14.8° (c 1.2, CH_3OH).

ACKNOWLEDGEMENTS

The authors would like to thank Dr. Timothy Shea of Temple University for technical assistance.

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