Arch Pharm Res Vol 28, No 1, 16-21, 2005

Archives of Pharmacal Research
http://apr.psk.or.kr

Synthesis and Conformational Study of 2-Trityloxymethyltetrahydrofurans as Key Intermediates for Antiviral Nucleosides

Hye-Young Choi and Hee-Doo Kim

College of Pharmacy, Sookmyung Women's University, Seoul 140-742, Korea

(Received November 6, 2004)

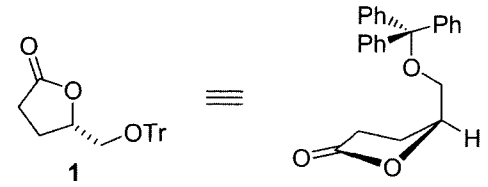
We wanted to elucidate the reason why the trityloxymethyl substituent in γ-trityloxymethyl-γ-butyrolactone takes a sterically unfavorable specific conformation, and so we synthesized 5-trityloxymethyldihydrofuran-3-one, 3-(trityloxymethyl)-4-butanolide and 2-trityloxymethyl-tetrahydrofuran and we then analyzed their conformation by ^{1}H-NMR analysis.

Key words: γ-Trityloxymethyl-γ-butyrolactone, Conformational analysis, Vicinal coupling constant, *Gauche* effect, Electrostatic interaction, Antiviral nucleoside

INTRODUCTION

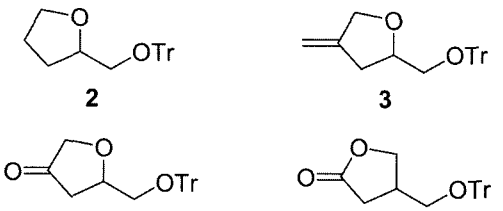
(*S*)-γ-Trityloxymethyl-γ-butyrolactone (**1**) (Takano *et. al.*, 1981) and its analogs are widely used as chiral building blocks for the synthesis of optically active compounds. (Coppola *et.al.*, 1987) Their ability to control the relative and absolute stereochemistry in the construction of contiguous tertiary and quarternary carbon centers by a highly controlled 1,3- and 1,4-asymmetric induction is extremely valuable for the synthesis of enantiomerically pure natural products. (Tomioka *et.al.*, 1985) and versatile chiral sugars for antiviral nucleosides (Agrofolio *et al.*, 1998). The origin of the high stereoselectivity displayed by **1** is mainly attributable to its specific conformation, in which the bulky trityloxymethyl group is folded over the lactone ring, as is shown in Fig. 1 (Tomioka *et.al.*, 1988).

For elucidating the reason why the trityloxymethyl substituent in γ-trityloxymethyl-γ-butyrolactone takes a sterically unfavorable conformation, we have synthesized the following trityloxymethyl compounds including 2-trityloxymethyltetrahydrofuran (**2**), 4-methylene-2-trityloxymethyltetrahydrofuran (**3**), 5-trityloxymethyldihydrofuran-3-one (**4**) and 3-(trityloxymethyl)-4-butanolide (**5**), and we analyzed their conformations by ^{1}H-NMR analyses.



1

Fig. 1. Structure of γ-trityloxymethyl-γ-butyrolactone



2 **3** **4** **5**

Fig. 2. Structures of trityloxymethyltetrahydrofurans

MATERIALS AND METHODS

The melting points for the compounds were obtained using a hot-stage microscope and they were the uncorrected values. The ^{1}H-NMR spectra were obtained on a Brucker WP 80 SY spectrometer, a GEMINI 300 spectrometer or a Varian 400 spectrometer, and the chemical shifts are reported as values in parts per million (δ) relative to tetramethylsilane (TMS) as an internal standard. The UV spectra were recorded with the use of a Shimadzu UV-2101PC spectrophotometer. The infrared spectra (IR) were recorded on a Shimadzu IR-430 spectrophotometer. The EI mass (EIMS) spectra were run on a VG Trio-2 GC-MS spectrometer at 70 eV. Thin layer chromatography

Correspondence to: Hee-Doo Kim, Sookmyung Women's University, College of Pharmacy, 53-12 Chungpa-Dong, Yongsan-Ku, Seoul 140-742, Korea
Tel: 82-2-710-9567, Fax: 82-2-703-0736
E-mail: hdkim@sookmyung.ac.kr

(TLC) was carried out on 0.25 mm E. Merck precoated silica gel glass plates ($60F_{254}$). Column chromatography was performed using the forced flow of the indicated solvent on Merck Kieselgel 60 (230~400 mesh). Unless otherwise noted, all the materials were obtained from commercially available sources and they were used without further purification. Tetrahydrofuran (THF) was freshly distilled from sodium benzophenone ketyl under an argon atmosphere. Methylene chloride, benzene, dimethylformamide (DMF), triethylamine (TEA) and toluene were freshly distilled under a nitrogen atmosphere with calcium hydride.

Tetrahydro-2-(trityloxymethyl)furan (2)

Triphenylmethyl chloride (2,300 mg, 8.22 mmol) was added to a stirred solution of tetrahydrofurfuryl alcohol (700 mg, 6.85 mmol) in 15 mL of pyridine. After stirring for 20 h at 70 °C, the reaction was quenched with water and the products were extracted with ethyl acetate. The organic layer was washed several times with aqueous $CuSO_4$ solution, and then this was washed with water and brine, dried over sodium sulfate, filtered and concentrated to furnish the pale yellow solid. Purification of the crude solid by silica gel chromatography (hexane/AcOEt=15:1) yielded 3,316 mg (97%) of **2** as a solid: mp 82-83 °C; IR (melt) cm^{-1} 1200, 1080; ^{1}H-NMR (100 MHz, $CDCl_3$) δ 7.1-7.6 (m, 15H), 4.0-4.2 (m, 1H), 3.75-3.95 (m, 2H), 3.05 (dd, *J* = 9.5, 5.5 Hz, 1H), 3.14 (dd, *J* = 9.5, 4.9 Hz, 1H), 1.5-2.1 (m, 4H).

Triphenylmethyl allyl ether (6)

Allyl chloride (12.20 mL, 180.07 mmol) was added to a stirred solution of triphenylmethyl chloride (50,200 mg, 180.07 mmol) in pyridine. After stirring for 1 day at room temperature, the reaction was concentrated and then rediluted with ethyl acetate. The organic layer was washed several times with aqueous $CuSO_4$ solution, and then it was washed with water and brine, dried over sodium sulfate, filtered and concentrated to yield 45.28 g (83.7%) of **6** as a pale yellow solid. The finely divided solid was washed several time with hexane and directly used for the next reaction: mp 68-70 °C; IR (melt) cm^{-1} 3060, 3011, 2862, 1646, 1597; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.53-7.49 (m, 5H), 7.36-7.27 (m, 10H), 6.04-5.93 (m, 1H), 5.50-5.43 (m, 1H), 5.23-5.18 (m, 1H), 3.68-3.65 (m, 2H); MS (EI) *m/z* 301 (MH^+, 2), 300 (M^+, 9), 243(100).

3-Trityloxypropane-1, 2-diol (7)

OsO_4 (30 mg) was added to a stirred mixture of **6** (18,000 mg, 59.92 mmol) and 4-methylmorpholine *N*-oxide (7,720 mg, 65.91 mmol) in 20% aqueous acetone at 0 °C. After stirring for 4 h at room temperature, the reaction mixture was quenched with sodium hydrosulfite (1,000 mg). 10 g of silica gel mixed in water was added, and the resulting mixture was stirred, filtered through a pad of celite, evaporated, and then diluted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated to a dry state. Purification of the residue by silica gel chromatography (hexane/AcOEt=3:1) yielded 15.12 g (75.4%) of **7** as a pale yellow solid: mp 103-105 °C; IR (neat) cm^{-1} 3397, 3060, 3021, 2930, 1597; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.49-7.46 (m, 5H), 7.36-7.25 (m, 10H), 3.89-3.88 (m, 1H), 3.72-3.59 (m, 2H), 3.32-3.22 (m, 2H), 2.82 (s, 1H), 2.41 (s, 1H); MS (EI) *m/z* 334 (M^+, 5) 259 (23), 243 (100).

1-(*tert*-Butyldimethylsilanyloxy)-3-trityloxypropan-2-ol (8)

tert-Butyldimethylsilyl chloride (1,360 mg, 9.03 mmol) was added to a stirred mixture of **7** (3,020 mg, 9.03 mmol) and imidazole (1,230 mg, 18.06 mmol) in THF at 0 °C. After stirring for 1 h at room temperature, the reaction mixture was diluted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated to a dry state. Purification of the residue by silica gel chromatography (hexane/AcOEt = 30:1) yielded 3.61 g (90.0%) of **8** as a colorless oil: IR (neat) cm^{-1} 3460, 3060, 3023, 2928, 1597; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.42-.7.39 (m, 5H), 7.28-7.19 (m, 10H), 3.84-3.73 (m, 1H), 3.66 (d, *J* = 4.0 Hz, 1H), 3.65 (d, *J* = 4.0 Hz, 1H), 3.19 (dd, *J* = 9.3, 5.6 Hz, 1H), 3.12 (dd, *J* = 9.3, 5.6Hz, 1H), 2.39 (d, *J* = 5.2 Hz, 1H), 0.81 (s, 9H), 0.00 (s, 6H); MS (FAB) *m/z* 448 (M^+), 243 (100).

***tert*-Butyldimethyl (2-prop-2-ynyloxy-3-trityloxy-propoxy) silane (9)**

The alcohol **8** (1,460 mg, 3.25 mmol) and 15-crown-5 (30 μL) were added to a suspension of NaH (74 mg, 50% in oil) in toluene. After stirring for 2 h at 70 °C, the reaction was cooled to 0 °C. After the addition of propargyl bromide (80%, 2.9 mL, 26.02 mmol), the reaction mixture was stirred for 12 h, quenched with aqueous NH_4Cl, and the resulting products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated. Purification of the residue by silica gel chromatography (hexane/AcOEt = 150:1) yielded 1350 mg (85.3%) of **9** as a colorless oil: IR (neat) cm^{-1} 3306, 3060, 3023, 2928, 1597; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.47-7.43 (m, 5H), 7.30-7.21 (m, 10H), 4.33 (d, *J* = 1.2 Hz, 1H), 4.32 (d, *J* = 1.2 Hz, 1H), 3.81-3.63 (m, 3H), 3.20 (d, *J* = 1.2 Hz, 1H), 3.19 (d, *J* = 2.0 Hz, 1H), 2.39 (t, *J* = 2.4 Hz, 1H), 0.81 (s, 9H), 0.00 (s, 6H); MS (FAB) *m/z* 486 (M^+, 2), 243.

2-Prop-2-ynyloxy-3-trityloxypropan-1-ol (10)

Bu_4NF (1M solution in THF, 1.58 mL, 1.58 mmol) was

added to a stirred solution of **9** (383 mg, 0.79 mmol) in THF. After stirring for 1 h, the reaction mixture was concentrated to a dry state. Purification of the residue by silica gel chromatography (hexane/AcOEt=10:1) yielded 244 mg (87.4%) of **10** as a colorless oil: IR (neat) cm^{-1} 3451, 3305, 3016, 2925, 1598; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.37-7.34 (m, 5H), 7.22-7.14 (m,10H), 3.72-3.53 (m, 3H), 3.20 (dd, *J* = 10.0, 5.1 Hz, 1H), 3.14 (dd, *J* = 10.0, 5.1 Hz, 1H), 1.90 (s, 1H); MS (EI) *m/z* 372 (M^+), 259 (9), 243 (100).

Triphenylmethyl 3-iodo-2-(prop-2-ynyloxy)propyl ether (12)

Methanesulfonyl chloride (0.89 mL, 11.46 mmol) was added to a stirred mixture of **10** (580 mg, 1.64 mmol) and triethylamine (2.74 mL, 19.64 mmol) in CH_2Cl_2 at 0 °C. After stirring for 2 h at room temperature, the reaction mixture was concentrated to a dry state to yield the mesylate **11**, and this was directly used for the next reaction without any purification. NaI (4,400 mg, 29.35 mmol) was added to a stirred solution of **11** in acetone and the reaction mixture was heated to reflux. After monitoring the reaction by TLC, the reaction was quenched with aqueous sodium thiosulfate solution, evaporated, diluted with ethyl acetate, and the products were extracted with ethyl acetate. The organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated to a dry state. Purification of the residue by silica gel chromatography (hexane/AcOEt=100:1) yielded 562 mg (73.9%) of **12** as a colorless oil: IR (neat) cm^{-1} 3060, 3031; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.36 (m, 5H), 7.26-7.16 (m, 10H), 4.17 (d, *J* = 1.1 Hz, 1H), 4.16 (d, *J* = 1.1 Hz, 1H), 3.54 (d, *J* = 5.4 Hz, 1H), 3.30 (m, 3H), 3.16 (dd, *J* = 9.9, 5.4 Hz, 1H), 2.33 (t, *J* = 2.4 Hz, 1H).

4-Methylene-2-trityloxymethyltetrahydrofuran (3)

Bu_3SnH (0.47 mL, 1.75 mmol) was added to a stirred mixture of **12** (543 mg, 1.17 mmol) and AIBN (15 mg) in toluene, and the reaction mixture was heated to reflux for 3 h. The reaction mixture was concentrated to a dry state. Purification of the residue by silica gel chromatography (hexane/AcOEt=200:1) yielded 310 mg (78.4%) of **3** as a colorless oil: IR (neat) cm^{-1} 3060, 2956, 1598; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.39-7.35 (m, 5H), 7.23-7.11 (m, 10H), 4.90-4.82 (m, 2H), 4.26 (m, 3H), 3.13 (dd, *J* = 9.6, 5.5 Hz, 1H), 3.03 (dd, *J* = 9.6, 4.7 Hz, 1H), 2.59-2.52 (m, 1H), 2.35-2.88 (m, 1H); MS (EI) *m/z* 356 (M^+), 243 (100).

5-Trityloxymethyldihydrofuran-3-one (4)

A gentle stream of dry ozone is passed through the stirred solution of **3** (232 mg, 0.68 mmol) in MeOH-CH_2Cl_2 at -78 °C. Ozonolysis was continued until the distinctive blue color of the excess ozone was first observed; ozonolysis was then terminated and the excess ozone was removed by purging with a stream of oxygen for 5-10 min. Dimethyl sulfide (0.5 mL) was then added. The resulting mixture was allowed to warm to room temperature over 2 h, and then it was concentrated. The residual solid was purified by silica gel chromatography (hexane/AcOEt=20:1) to yielded 70 mg (30%) of **4** as a solid: mp 127-128 °C; IR (KBr) cm^{-1} 3060, 3022, 2922, 1760, 1597; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 7.36-7.33 (m, 5H), 7.26-7.16 (m, 10H), 4.13 (d, *J* = 16.9 Hz, 1H), 3.89 (d, 1H, *J* = 16.9 Hz), 3.37 (dd, *J* = 10.1, 3.5 Hz, 1H), 3.14 (dd, *J* = 10.1, 4.2 Hz, 1H), 2.47 (dd, *J* = 18.0, 7.6 Hz, 1H), 2.35; HRMS (EI) calcd for $C_{24}H_{22}O_3$ (M^+) 358.1569, found 358.1569.

Bis-(*t*-butyldimethylsilyloxy)acetone (14)

t-Butyldimethylsilyl chloride (829 mg, 5.50 mmol) was added to a stirred mixture of 1,3-dihydroxyacetone dimer (197.5 mg, 1.10 mmol) and imidazole (597.1 mg, 8.77 mmol) in DMF. After stirring for 2 days at room temperature, the reaction was quenched with water and the products were extracted with hexane. The organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated to a dry state. Purification of the residue by silica gel chromatography (hexane/AcOEt=50:1) yielded 625mg (89.5%) of **14** as a colorless oil: IR (neat) cm^{-1} 2950, 2930, 2890, 1740; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 4.41 (s, 4H), 0.92 (s, 18H), 0.09 (s, 12H).

Ethyl 4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy)methyl]-2-butenoate (15)

A suspension of NaH (74 mg, 50% in oil) and triethyl phosphonoacetate (689 mg, 3.07 mmol) was stirred for 1 h at room temperature, and then **14** (753 mg, 2.56 mmol) was added. After stirring for 12 h at room temperature, the reaction was quenched with water and the products were extracted with hexane. The organic layer was washed with water and brine, dried over sodium sulfate, filtered and concentrated. Purification of the residue by silica gel chromatography (hexane/AcOEt=50:1) yielded 620 mg (74%) of **15** as a colorless oil: IR (neat) cm^{-1} 2930, 2900, 2860, 2830, 1710, 1650; ^{1}H-NMR (80 MHz, $CDCl_3$) δ 6.01 (m, 1H), 4.90 (br s, 2H), 4.46 (br s, 2H), 4.19 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H), 0.97 (s, 9H), 0.93 (s, 9H), 0.12 (s, 3H), 0.10 (s, 3H), 0.06 (6H); MS *m/z* 373 (MH^+), 345, 331, 147, 73.

Ethyl 4-(*t*-butyldimethylsilyloxy)-3-[(*t*-butyldimethylsilyloxy)methyl]butanoate (16)

15 (812 mg, 2.3 mmol) was dissolved in 5 mL of ethanol, and 5% palladium on carbon (10 mg) was added. The reaction vessel was fitted with a three-way stopcock and a hydrogen-filled balloon was attached. The remaining inlet was attached to a vacuum (20 mmHg), and the reaction

vessel was carefully evacuated until the solvent had just began to boil. The reaction vessel was then filled with H_2 gas from the balloon. This procedure was repeated twice. The reaction was then stirred under an excess of H_2 (balloon pressure). After 24 h, the reaction was filtered through a pad of celite, and the filtrate was concentrated. Purification of the residue by silica gel chromatography (hexane/AcOEt=50:1) yielded 801 mg (93%) of **16** as a colorless oil: IR (neat) cm^{-1} 2930, 2900, 2700, 1740; ^{1}H-NMR (300 MHz, $CDCl_3$) δ 4.13 (q, *J* = 7.2 Hz, 2H), 3.60 (dd, *J* = 5.7, 1.5 Hz, 4H), 2.33 (d, *J* = 6.9 Hz, 2H), 2.17 (m, 1H), 1.26 (t, *J* = 7.2 Hz, 3H), 0.91 (s, 18H), 0.04 (s, 8H), 0.01 (s, 4H); MS *m/z* 375 (MH^+), 345, 333, 305.

3-Hydroxymethyl-4-butenolide (17)

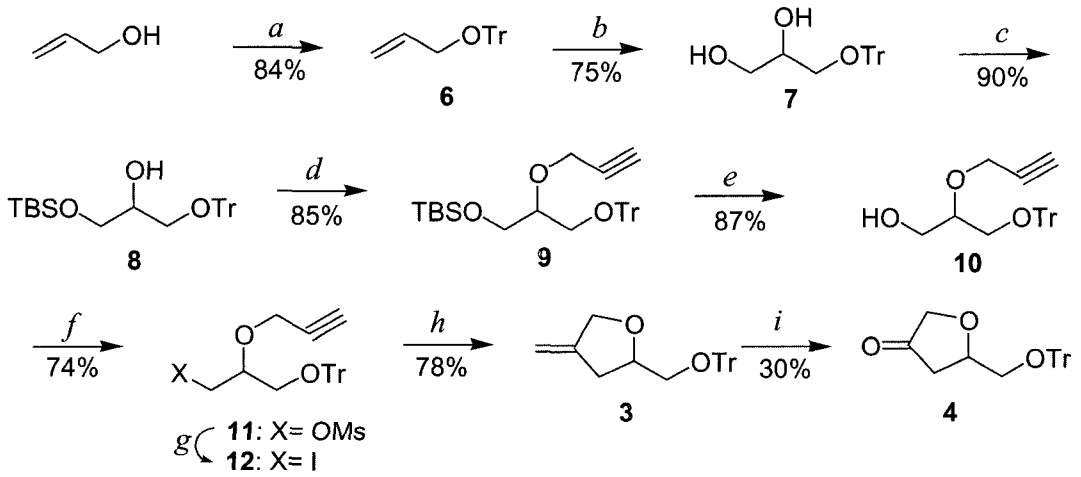
n-Bu_4NF (1.0 M solution in THF, 3.7 mL, 3.70 mmol) was added to a stirred solution of **16** (469 mg, 1.25 mmol) in THF. After stirring for 1 day at room temperature, the mixture was then concentrated. Purification of the residue by silica gel chromatography (hexane/AcOEt=2:1) yielded 112 mg (77%) of **17** as a colorless oil: IR (neat) cm^{-1} 3400, 2900, 1760; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 4.35 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.16 (dd, *J* = 9.2, 5.2 Hz, 1H), 3.66 (dd, *J* = 10.8, 4.8 Hz, 1H), 3.16 (dd, *J* = 10.8, 6.8 Hz, 1H), 2.72 (m, 1H), 2.55 (dd, *J* = 17.6, 8.8 Hz, 1H), 2.33 (dd, *J* = 17.6, 6.0 Hz, 1H), 1.93 (br s, 1H) ; MS *m/z* 117 (MH^+,5), 98 (5), 86 (7), 74 (40), 70 (22), 57 (100).

3-(Trityloxymethyl)-4-butanolide (5)

Triphenylmethyl chloride (120 mg, 0.43 mmol) was added to a stirred solution of **17** (50 mg, 0.43 mmol) in 2 mL of pyridine. After stirring for 2 days at room temperature, the reaction was quenched with water and extracted with ethyl acetate. The organic layer was washed several times with aqueous $CuSO_4$ solution. The organic layer was then washed with water and brine, dried over sodium sulfate, filtered and concentrated to furnish the pale yellow solid. Purification of the crude solid by silica gel chromatography (hexane/AcOEt=5:1) yielded 142 mg (93%) of **5** as a solid: mp 154 °C (a colorless needle from 30% AcOEt in hexane); IR (KBr) cm^{-1} 3080, 3050, 2970, 2900, 1770; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.4-7.1 (m, 15H), 4.37 (dd, *J* = 9.2, 7.2 Hz, 1H), 4.09 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.16 (dd, *J* = 9.2, 6.0 Hz, 1H), 3.08 (dd, *J* = 9.2, 6.8 Hz, 1H), 2.74 (m, 1H), 2.53 (dd, *J* = 17.6, 8.8 Hz, 1H), 2.27 (dd, 17.6, 6.4 Hz, 1H), HRMS (EI) *calcd for* $C_{24}H_{22}O_3$ (M^+) 358.1569, found 358.1567.

RESULTS AND DISCUSSION

To investigate the role of the carbonyl group on the butyrolactone ring, we designed 2-trityloxymethyltetrahydrofuran (**2**) as a first target, and this was synthesized very simply by the tritylation of a commercially available 2-tetrahydrofurfuryl alcohol. Next, as a nonpolar substitute for the polar carbonyl group on **1**, 4-methylene-2-trityloxymethyltetrahydrofuran (**3**) was chosen and prepared according to the Scheme 1. Triphenylmethyl allyl ether (**6**) was obtained from allyl alcohol and triphenylmethyl chloride in pyridine, and it was treated with OsO_4 to furnish the diol **7** in 75% yield. Selective protection of primary hydroxyl group was done with TBSCl, and this was followed by *O*-alkylation with propargyl bromide, which gave us a good yield of the ether **9**. Deprotection of **9** with TBAF in THF gave us an 87% yield of the alcohol **10**, and the resulting primary alcohol **10** was then transformed to the iodide **12** *via* a two step sequence with 74% yield. Finally, the crucial radical cyclization was accomplished by a treatment of **12** with tributyltin hydride in toluene, which gave us a 78% yield of **3**. Transposition



Scheme 1. Reagents and conditions: a) triphenylmethyl chloride, pyridine; b) OsO_4, NMO, acetone-H_2O; c) TBSCl, imidazole,THF; d) NaH, 15-crown-5, propargyl bromide, toluene; e) TBAF, THF; f) MsCl, TEA, CH_2Cl_2; g) NaI, acetone; h) Bu_3SnH, AIBN, toluene; i) O_3,CH_2Cl_2, MeOH.

of carbonyl group in **1** to the next position resulted in the more polar ketone **4**. We could get some information from this transposition as to whether the ester functionality is crucial or not for taking a special conformation. 5-Trityloxymethyldihydrofuran-3-one (**4**) was prepared from ozonolysis of the alkene **3**.

Compound **5** was also selected as a probe for investigating the *gauche* effect, and it was prepared according to the Scheme 2. A commercially available dihydroxyacetone dimer was treated with TBSCl to give a 90% yield of ketone **14**. Horner-Wadsworth-Emmons olefination of **14** with triethyl phosphonoacetate and NaH in DMF gave a 74% yield of the ester **15**. Subsequent hydrogenation of **15** followed by desilylation gave the cyclized lactone **17** in a good yield. Tritylation of **17** with TrCl in pyridine gave a 93% yield of the lactone **5**.

After completion of the synthesis, we turned our attention to analyzing the conformation of the target molecules. The conformational analysis of a series of the trityloxymethyltetrahydrofurans (**1-5**) was performed with the coupling constants of their ^{1}H-NMR spectra. When the trityloxymethyl group on the tetrahydrofurans (**1-5**) is rotated from 0° to 360°, there are three local minimal staggered conformers ***A***, ***B*** and ***C*** (Fig. 3).

The relative configuration of the protons deduced from the vicinal coupling constant (J_{ax}/J_{bx}) confirmed the conformation of trityloxymethyl substituent of the compound. According to the Karplus equation, conformer ***A***, having 60° of dihedral angle between H_x and two protons (H_a, H_b), was expected to show small coupling constants around 3.5 Hz. In contrast, one of the two protons in both the ***B*** and ***C*** conformers should be positioned *anti* to H_x with 180° of dihedral angle. Thus, these two conformers were expected to show the larger coupling constants. The coupling constant will be observed differently depending on the conformational equilibrium;, that is, it depends on the individual value of any conformer and its mole fraction (n). In other words, the observed J_{ax} or J_{bx} value reflects the percent ratio of each conformer.

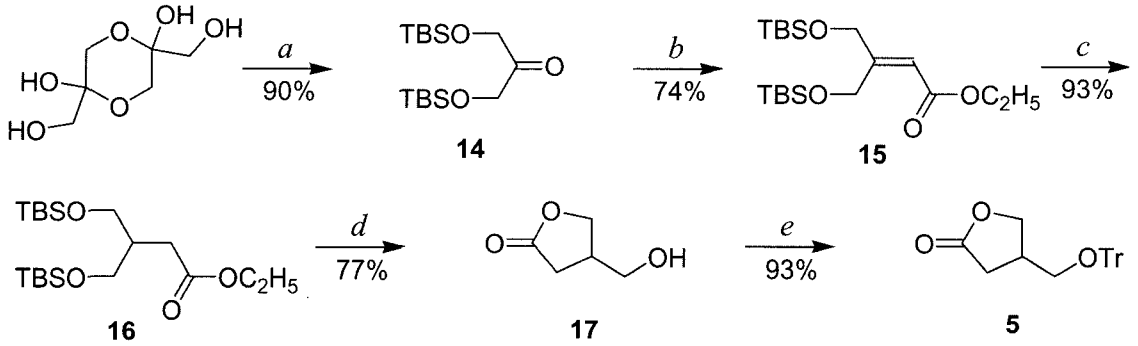
$$J_{ax(observed)} = n_A J_{A\,ax} + n_B J_{B\,ax} + n_C J_{C\,ax} \quad (1)$$

$$J_{bx(observed)} = n_A J_{A\,bx} + n_B J_{B\,bx} + n_C J_{C\,bx} \quad (2)$$

$$1 = n_A + n_B + n_C \quad (3)$$

The vicinal coupling constants for each staggered conformation obtained from the energy minimization process were then calculated by using the modified Karplus equation. (Haasnoot *et al.*, 1980) As a consequence of the fast interconversion of the conformers, the observed coupling constants are weighed averages. The ratio of the three conformers can be calculated from the comparison of the observed and calculated coupling constants. The results of population analysis from the coupling constants are presented in Table I.

In compounds **1-4** (X=O), the *gauche* conformers ***A*** and ***B*** predominate over the *anti* conformer ***C***. In contrast, compound **5** (X= CH_2) shows a different trend in which the sterically more stable conformers ***B*** and ***C*** predominate over the conformer ***A***. These two things can be well



Scheme 2. Reagents and conditions: a) TBSCl, imidazole, DMF; b) $(EtO)_2POCH_2CO_2Et$, NaH, DMF; c) H_2, Pd/C, EtOH; d) Bu_4NF, THF; e) triphenylmethyl chloride, pyridine

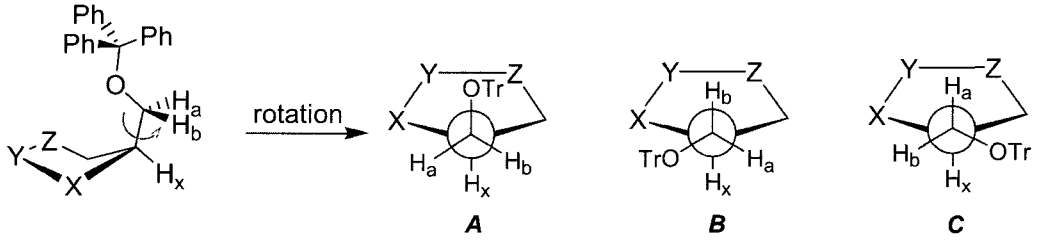


Fig. 3. Staggered conformers of trityloxymethyltetrahydrofurans

Table I. Vicinal Coupling Constant (Hz) and % population of ***A***, ***B*** and ***C***

Compound	J_{ax}	J_{bx}	% population at 25 °C		
			A	B	C
1	3.4	4.4	66	28	6
2	4.9	5.5	33	37	30
3	4.7	5.5	35	38	27
4	3.5	4.2	68	26	6
5	6	6.8	14	45 (41)	41 (45)

explained by the favorable *gauche* effect. (Wolfe *et al.*, 1972) However, the most notable phenomenon is that the sterically unfavorable conformer ***A*** predominates over the conformer ***B*** in compounds **1** and **4**. In conformer ***A***, the C-O bond of the bulky trityloxymethyl group is positioned *anti* to the C-Hx bond, an unusual alignment considering the unfavorable steric interactions that are present. This unexpected preference for conformer ***A*** could not be explained by only the *gauche* effect. An additional stabilizing factor may be operating in the system. These two compounds (**1** and **4**) share the following things in common; First, they both have O-C-C-O bond arrangements that are favorable for the *gauche* effect. Second, they both have a carbonyl group. As the *gauche* effect is evidently present, we focused our attention on the carbonyl functionality. When the carbonyl group was removed, as shown in compound **2**, the conformer ***A*** mole fraction dropped from 0.6 to 0.3. Despite the minimal structural disturbance from **4** to **3**, the ratio of conformer ***A*** was also decreased dramatically. The polar character of the carbonyl group seems to be very important to the specific conformation. Thus, when coupled with *gauche* effect, the electrostatic interactions between the positive charge on the carbonyl carbon and the negative charge on the oxygen in the trityloxymethyl group are likely to be operative for the compound **1** to take the unusual conformation (Morimoto *et. al.*, 1997).

In summary, we have synthesized the four trityloxymethyl compounds including 2-trityloxymethyltetrahydrofuran (**2**), 4-methylene-2-trityloxymethyltetrahydrofuran (**3**), 5-trityloxymethyldihydrofuran-3-one (**4**) and 3-(trityloxymethyl)-4-butanolide (**5**), and we analyzed their conformations by ^{1}H-NMR analyses. Coupled with *gauche* effect, the additional electrostatic interaction seems to be operative for the compound **1** to take the unusual conformation.

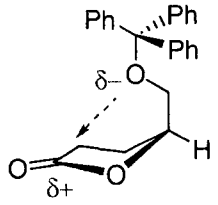


Fig. 4. Electrostatic interaction

ACKNOWLEDGEMENT

This research was supported by the Sookmyung Women's University Research Grants 2004.

REFERENCES

Agrofolio, I. A. and Challand, S. R., Acyclic Carbocyclic and L-Nucleosides. Kluwer Academic Publisher: Dordrecht. Boston, Lodon, 1998.

Coppola, G. M. and Schuster, H. F., *Asymmetric Synthesis: Construction of chiral molecules using amino acids.* John Wiley & Sons, Inc., New York, 1987.

Haasnoot, C. A. G., De Leeuw, F. A. A. M., and Altona, C., The relationship between proton-proton NMR coupling constants and substituent electronegativities-1. *Tetrahedron*, 36, 2783-2792 (1980).

Morimoto, Y. and Shirahama, H., Unexpected stability of γ-lactone with axial substituents rather than equatorial ones. Conformational evaluation by molecular mechanics and molecular orbital calculations. *Tetrahedron*, 53, 2013-2024 (1997).

Takano, S., Yonaga, M., and Ogasawara, K., Synthesis of both enantiomers of γ-(trityloxymethyl)-γ-butyrolactone from a single progenitor, (*S*)-(+)-glutamic acid. *Synthesis*, 4, 265-266 (1981).

Tomioka, K., Kawasaki, H., and Koga, K., Control elements in the asymmetric tandem alkylation of α-alkylidene-γ-butyrolactone derivatives. *Tetrahedron Lett.*, 26, 3027-3030 (1985).

Tomioka, K., Kawasaki, H., Iitaka, Y., and Koga, K., Enantiospecific total synthesis of (-)-megaphone by a highly controlled consecutive 1,4- and 1,3-asymmetric induction. *Tetrahedron Lett.*, 26, 903-906 (1985).

Tomioka, K., Cho, Y.-S., Sato, F., and Koga, K., Stereoselective reaction 14. Efficient Enantioselective construction of quaternary carbon center by sequential dialkylation of (*S*)-γ-[(Trityloxy)methyl]-γ-butyrolactone. Synthesis of optically active β,β-disubstituted γ-lactones. *J. Org. Chem.*, 53, 4094-4098 (1988).

Wolfe, S., Gauche effect. Stereochemical consequences of adjacent electron pairs and polar bonds. *Acc. Chem. Res.*, 5, 102-111 (1972).