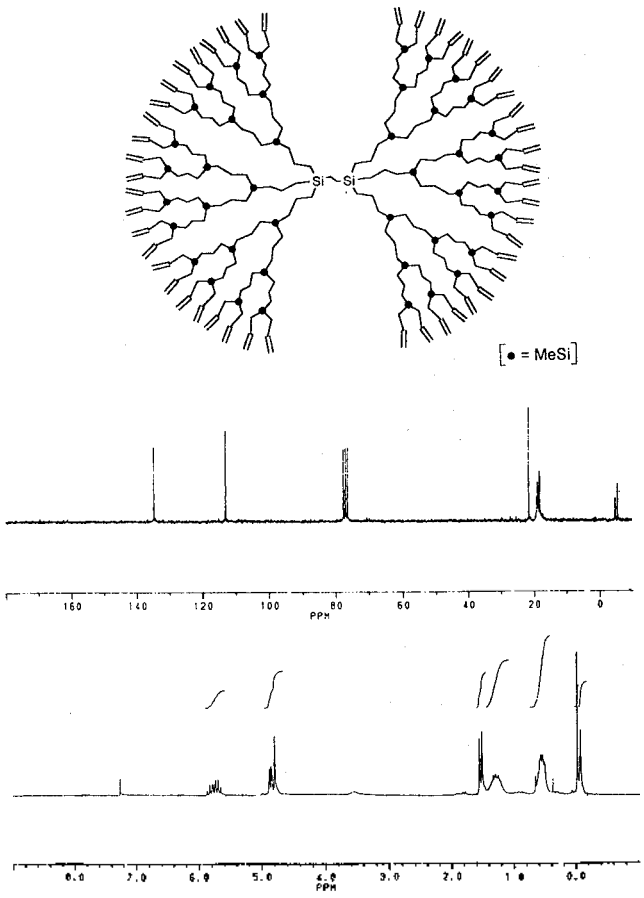

Figure 1. The Schematic View of 3rd Generation of Dendrimeric Silane with 48 Allylic End Groups and its ^{13}C (up) and ^{1}H (down) NMR Spectra.

17-19 ppm for CH_2 signals to assist in controlling the reaction and detecting the exsisting small amounts of impurities which exist in the reaction mixture. Elemental compositon of the dendrimers (Gn generation) determined by combustion is very close to the expected value (Table 1).

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Reaction of Nitrile Oxides with 3(2*H*)- and 2(5*H*)-Furanones

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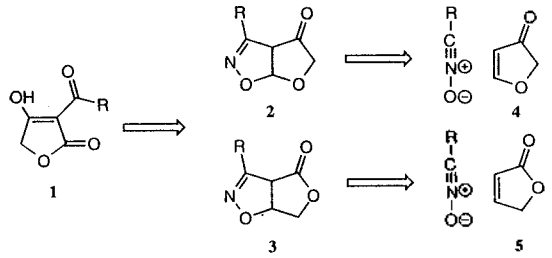
1,3-Dipolar cyclization of various nitrile oxides with 3(2*H*)- and 2(5*H*)-furanones regioselectively furnished the corresponding syn-addition products of 3-oxotetrahydro-furano[4,5-*d*]isoxazolines and 2-oxotetrahydrofurano[3,4-*d*]isoxazolines.

Introduction

Nitrile oxides are reactive 1,3-dipoles, which add to ethylenic and acetylenic dipolarophiles with high regioselectivity to furnish Δ^2-isoxazolines and isoxazoles, respectively. These stereoselectively controlled reaction intermediates serve as useful building blocks that lead to various compounds through chemical modification and ring cleavage. For exam-



Scheme 1.

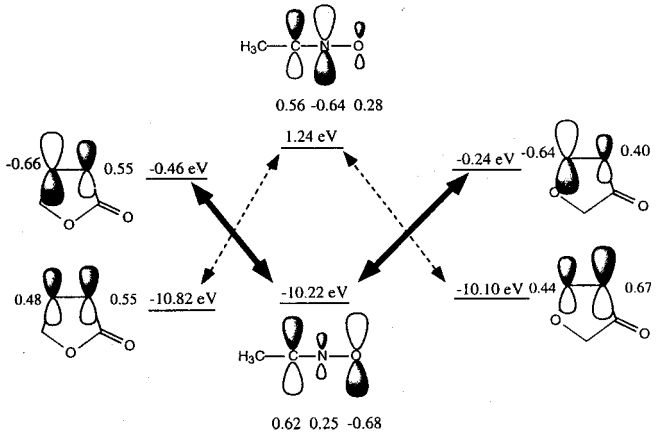
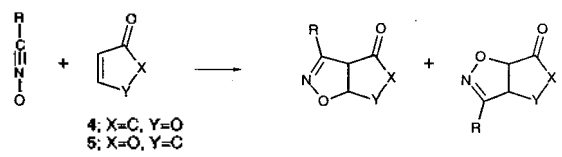


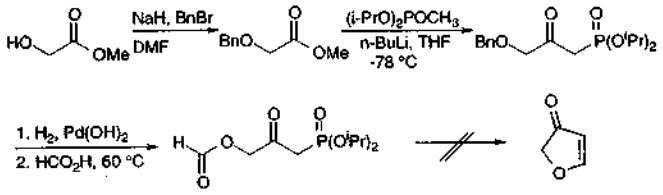
Figure 1. Frontier Orbital Interactions between Acetonitrile Oxide and 3(2*H*)- and 2(5*H*)-Furanones.

ple, the cleavage of the isoxazoline rings derived from ethylenic dipolarophiles provides a variety of acyclic compounds such as α,β-unsaturated ketones, β-hydroxyketones, and γ-amino alcohols.[1] The stereochemical outcome for cycloaddition between nitrile oxide and dipolarophile can be explained in terms of frontier orbitals.[2] Cycloaddition of nitrile oxides with monosubstituted electron deficient ethylenic dipolarphiles results from the HOMO (dipole)+LUMO (dipolarophile) interaction. Reactions with electron rich or conjugated dipolarophiles are controlled by the LUMO (dipole)-HOMO (dipolarophile) interaction. More specifically inside-outside stereochemical effect for 1,3-dipolar cycloaddition was applied to the transitional states.[3]

In an effort toward the synthesis of acyltetronic acid derivatives (**1**), we became interested in the 1,3-dipolar reaction of 3(2*H*)- and 2(5*H*)-furanones (**4** and **5**) and nitrile oxides (Scheme 1). In general, cycloaddition of nitrile oxides with open-chain α,β-unsaturated esters furnishes a mixture of regioisomeric products.[4] Likewise it is possible that products may exist as a regioisomeric mixture from the reactions of 3(2*H*)- and 2(5*H*)-furanones with nitrile oxides.



However, in order to predict the regioselectivity for this reaction, we performed the semi-empirical quantum mechanical calculation for the frontier orbitals of 3(2*H*)- and 2(5*H*)-furanones on the PM3 level. The results confirm the regioselectivity as we expected (Figure 1).

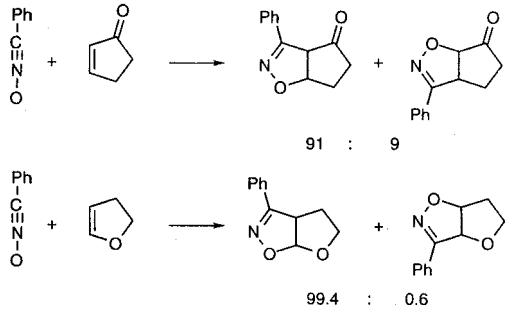


Scheme 2.

Thus we became encouraged by this computational prediction and decided to accomplish the synthetic survey to examine the scope and limit of this reaction.

Results and Discussion

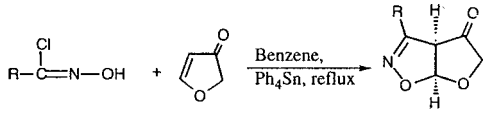
Reaction of Nitrile Oxides with 3(2*H*)-Furanones. It has been reported in the literature that the cycloaddition reaction of benzonitrile oxide with cyclopentenone and 2,3-dihydrofuran gave different major regioisomers.[5,6]



We thought that the cycloaddition reaction of 3(2*H*)-furanone (**4**) with nitrile oxdides would give excellent regioselectivity because of matching effects of a carbonyl group and an oxygen atom in the ring of **4**. 3(2*H*)-Furanone derivatives were prepared by the methods reported in the literature.[7,8] First of all, 3(2*H*)-furanone was prepared from epichlorohydrin by five step reactions. The reaction pathway required some tricky techniques such as flash distillation so that we attempted an alternative reaction pathway as shown in Scheme 2. Unfortunately the final step along the reaction sequence did not work as we had planned. The failure to cyclization was brought about by the facile cleavage of formate ester linkage. Thus we went back to the known method to prepare 3(2*H*)-furanone.

The preparation of nitrile oxides for the reaction with 3(2*H*)-furanone (**4**) was carried out by general methods such as dehydration reaction of nitro compounds with an aromatic isocyanates in the presence of triethylamine,[9] the reaction of oximes with NaOBr in the presence of a base,[10] and the reaction of chlorooximes (hydroximoyl chlorides) with a base.[11] However, we could not obtain the desired products under these conditions partly because of furoxans generated from the spontaneous dimerization of the nitrile oxides and partly because of instability of 3(2*H*)-furanone itself. Furthermore, the reaction between the nitrile oxides and 3(2*H*)-furanone

Table 1. 1,3-Dipolar Cycloaddition Reaction of 3(2*H*)-Furanone and Hydroximoyl Chlorides

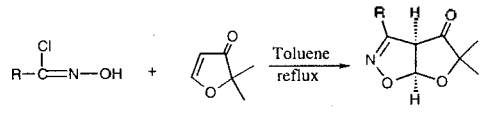


4 2

Entry	R	Yield of **2** (%)
1		35 (**2a**)
2		N.R. (**2b**)
3		52 (**2c**)
4		41 (**2d**)*

*Refluxed in toluene

Table 2. 1,3-Dipolar Cycloaddition Reaction of 2,2-Dimethyl-2(2*H*)-Furanone and Hydroximoyl Chlorides



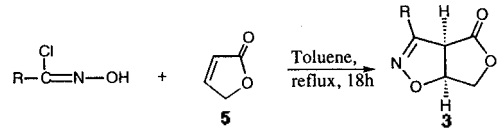
6 7

Entry	R	Yield of **7** (%)
1		67 (**7a**)
2		74 (**7b**)
3		45 (**7c**)
4		53 (**7d**)

seemed slow. In order to circumvent this difficulty we decided to generate the nitrile oxides from chlorooximes by employing the use of tetraphenyltin[12] as a base or simple reflux in toluene.[13] The results are shown in Table 1. 1,3-Dipolar cycloaddition reaction was regio- and stereoselective. The ^{1}H NMR spectral data of the resulting 3-oxotetrahydrofurano [4,5-*d*]isoxazolines show two doublet peaks at about 4.0 and 6.5 ppm for 4-H and 5-H, respectively. The low yields were attributed to the decomposition and self-polymerization of unstable 3(2*H*)-furanone itself under the reaction conditions. This consequence incited us to prepare more stable 2,2-dimethyl-3(2*H*)-furanone from 3-hydroxy-3-methyl-2-butanone by 2 steps.[8] We found the *in situ* generation of nitrile oxides could be done by simple reflux in toluene. The results of cycloaddition with various aromatic nitrile oxides are shown in Table 2. When we performed the reactions with aliphatic nitrile oxides we could not get the desired products under various reaction conditions.

Reaction of Nitrile Oxides with 2(5*H*)-Furanone. In case of the reaction of nitrile oxides with commercially available and relatively stable 2(5*H*)-furanone, we could achieve the satisfactory yields as well as regioselectivity. The results are shown in Table 3. The structural determination was carried out by examining the spectral data of the 2-oxotetrahydrofurano[3,4-*d*]isoxazoline. ^{1}H NMR data show a doublet at 4.2 ppm corresponding to 3-H. Further exploitation of the isoxazoline ring cleavage of 2-oxotetrahydrofurano [3,4-*d*]isoxazolines toward tetronic acid derivatives will be reported later.

Table 3. 1,3-Dipolar Cycloaddition Reaction of 2(5*H*)-Furanone and Hydroximoyl Chlorides



5 3

Entry	R	Yield of **3** (%)
1	n-C_3H_7	96 (**3a**)
2		72 (**3b**)
3		65 (**3c**)
4		85 (**3d**)
5		71 (**3e**)
6		97 (**3f**)
7	n-C_8H_{17}	96 (**3g**)

Experimental Section

General Comments. Melting points were determined on a Thomas-Hoover Uni-Melt apparatus in capillary tubes and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-435 spectrophotometer. ^{1}H NMR spectra were obtained on Bruker AM-300 and Varian Gemini 200 NMR spectrometers and measured in $CDCl_3$ solution, unless otherwise stated, relative to Me_4Si, as an internal standard (d=0.00). Mass spectra were obtained on a Schimadzu GCMS-QP 1000 mass spectrometer at 70 eV and recorded herein (relative intensity and assignment). Elementary analysis was obtained on Perkin-Elemer 240C Elemental Analyzer. Unless otherwise indicated in a specific experiment, all of the chemicals used were reagent grade and no additional purification has been done. 2(5*H*)-Furanone and tetraphenyltin were purchased from Aldrich Chemical Co. and used without further purification. 3(2*H*)-Furanone[7] and 2,2-dimethyl-3(2*H*)-furanone[8] were prepared from the literature method. Toluene and benzene were distilled over sodium and stored over molecular sieves. Thin layer chromatography (TLC) was performed on Merck 60 F-254 glass plates without activation. Column chromatography procedures utilized silica gel (Merck, silica gel 60, 70-230 mesh).

1,3-Dipolar Cycloaddition Reaction of Nitrile oxide and Furanones

General Reaction of 3(2*H*)-Furanone (4) and Hydroximoyl Chlorides. To a solution of hydroximoyl chloride (1.24 mmol) in benzene (10 mL) was added 3(2*H*)-furanone (1.36 mmol) and Ph_4Sn (1.24 mmol) under the nitrogen atmosphere. The solution was refluxed for 18 hr and the solvent was evaporated *in vacuo* to give crude product, which was purified by column chromatography (silica gel, hexane : EtOAc=4 : 1) to provide pure isoxazoline.

3-Isopropyl-3-oxotetrahydrofurano[4,5-*d*]isoxazoline (2a): yellow oil; ^{1}H NMR δ 1.22 (*d*, *J*=6.7 Hz, 3H), 1.30 (*d*, *J*=6.7 Hz, 3H), 2.71 (heptet, *J*=6.7 Hz, 1H), 4.01 (*d*, *J*=6.5 Hz, 1H), 4.15 (*s*, 2H), 6.53 (*d*, *J*=6.1 Hz, 1H); IR (neat) ν_{max} 1741, 1121 cm^{-1}; MS (rel. intensity) *m/z* 170 (M^++1, 8.3) 169 (M^+, 14.5), 85 (100), 41 (62).

3-Cyclohexyl-3-oxotetrahydrofurano[4,5-*d*]isoxazoline (2c): yellow oil; ^{1}H NMR δ 1.17-1.41 (*m*, 4H), 1.42-2.08 (*m*, 6H), 2.41 (*m*, 1H), 3.99 (*d*, *J*=6.4 Hz, 1H), 4.10 (*s*, 2H), 6.49 (*d*, *J*=6.1 Hz, 1H); IR (neat) ν_{max} 1735, 1116 cm^{-1}; MS (rel. intensity) *m/z* 210 (M^++1, 1.5), 209 (M^+, 5.3), 85 (100), 41 (58).

3-(2-Chlorophenyl)-3-oxotetrahydrofurano[4,5-*d*]isoxazoline (2d): yellow oil; ^{1}H NMR δ 4.12 (*d*, *J*=10.3 Hz, 1H), 4.25 (*d*, *J*=10.3 Hz, 1H), 4.70 (*d*, *J*=6.6 Hz, 1H), 6.67 (*d*, *J*=6.7 Hz, 1H), 7.36 (*m*, 4H); IR (neat) ν_{max} 1742, 1138 cm^{-1}; MS (rel. intensity) *m/z* 237 (M^+, 1.0), 182 (M^+, 100), 180 (100), 179 (70), 153 (78.5), 90 (42.6).

General Reaction of 2,2-Dimethyl-3(2*H*)-furanone and Hydroximoyl Chlorides. To a solution of hydroximoyl chloride (1.00 mmol) in toluene (5 mL) was added 2,2-dimethyl 3(2*H*)-furanone (1.50 mmol) under the nitrogen atmosphere. The solution was refluxed for 18 hr and the solvent was evaporated *in vacuo* to give crude product, which was purified by column chromatography (silica gel, hexane : EtOAc=4 : 1) to provide pure isoxazoline.

3-(2-Chlorophenyl)-2,2-dimethyl-3-oxotetrahydrofurano[4,5-*d*]isoxazoline (7a): mp 81-82 ℃; ^{1}H NMR δ 1.31 (*s*, 3H), 1.33 (*s*, 3H), 4.87 (*d*, *J*=6.8 Hz, 1H), 6.63 (*d*, *J*=6.7 Hz, 1H), 7.31-7.51 (*m*, 4H); IR (KBr) ν_{max} 1735, 1535, 1188 cm^{-1}; MS (rel. intensity) *m/z* 265 (M^+, 4.8), 246 (100), 155 (23.4), 127 (49.8).

3-(2-Methylphenyl)-2,2-dimethyl-3-oxotetrahydrofurano[4,5-*d*]isoxazoline (7b): mp 82-83 ℃; ^{1}H NMR δ 1.23 (*s*, 3H), 1.31 (*s*, 3H), 2.51 (*s*, 3H), 4.40 (*d*, *J*=6.6 Hz, 1H), 6.25 (*d*, *J*=6.6 Hz, 1H), 7.25 (*m*, 4H); IR (KBr) ν_{max} 1767, 1119 cm^{-1}; MS (rel. intensity) *m/z* 245 (M^+, 1.4), 162 (100), 163 (90.4), 135 (24.6), 45 (29.4).

3-(2,6-Dichlorophenyl)-2,2-dimethyl-3-oxotetrahydrofurano[4,5-*d*]isoxazoline (7c): mp 125-125.5 ℃; ^{1}H NMR δ 1.41 (*s*, 3H), 1.55 (*s*, 3H), 4.55 (*d*, *J*=7.0 Hz, 1H), 6.72 (*d*, *J*=7.0 Hz, 1H), 7.33 (*m*, 3H); IR (KBr) ν_{max} 1772, 1431, 1113 cm^{-1}; MS (rel. intensity) *m/z* 301 (M^++2, 1.9) 299 (M^+, 1.3), 214 (100), 213 (100), 212 (100), 185 (63.4).

3-Pyridyl-2,2-dimethyl-3-oxotetrahydrofurano[4,5-*d*]isoxazoline (7d): mp 42-43 ℃; ^{1}H NMR δ 1.15 (*s*, 3H), 1.23 (*s*, 3H), 4.35 (*d*, *J*=7.0 Hz, 1H), 6.52 (*d*, *J*=7.0 Hz, 1H), 7.25 (*m*, 1H), 8.15 (*m*, 1H), 9.00 (*m*, 1H); IR (KBr) ν_{max} 3006, 1762, 1173, 1115 cm^{-1}; MS (rel. intensity) *m/z* 232 (M^+, 1.2), 159 (34.3), 158 (84.1), 130 (100), 45 (39.8).

General Reaction of 2(5*H*)-Furanone (5) and Hydroximoyl Chlorides. To a solution of hydroximoyl chloride (1.53 mmol) in toluene (10 mL) was added 2(5*H*)-furanone (2.01 mmol) under the nitrogen atmosphere. The solution was refluxed for 18 hr and the solvent was evaporated *in vacuo* to give crude product, which was purified by column chromatography (silica gel, hexane : EtOAc=4 : 1) to provide pure isoxazoline.

3-Propyl-2-oxotetrahydrofurano[3,4-*d*]isoxazoline (3a): colorless oil; ^{1}H NMR δ 1.00 (*t*, *J*=7.3 Hz, 3H), 1.62-1.83 (*m*, 2H), 2.37-2.66 (*m*, 2H), 4.13 (*d*, *J*=9.6 Hz, 1H), 4.48 (*dd*, *J*=2.4 and 11.0 Hz, 1H), 4.63 (*dd*, *J*=5.8 and 11.0 Hz, 1H), 5.46 (*ddd*, *J*=2.4, 5.9, and 9.7 Hz, 1H); IR (neat) ν_{max} 1754, 1169 cm^{-1}; MS (rel. intensity) *m/z* 170 (M^++1, 14.2), 169 (M^+, 32.0), 141 (64.6), 110 (29.3), 97 (74.1), 85 (44.8), 43 (100).

3-Isopropyl-2-oxotetrahydrofurano[3,4-*d*]isoxazoline (3b): colorless oil; ^{1}H NMR δ 1.28 (*d*, *J*=6.7 Hz, 3H), 1.30 (*d*, *J*=6.7 Hz, 3H), 2.91 (heptet, *J*=6.7 Hz, 1H), 4.23 (*d*, *J*=9.4 Hz, 1H), 4.48 (*dd*, *J*=2.5 and 11.0 Hz, 1H), 4.64 (*dd*, *J*=5.8 and 11.0 Hz, 1H), 5.47 (*ddd*, *J*=2.5, 5.8, and 9.4 Hz, 1H); IR (neat) ν_{max} 1769, 1177 cm^{-1}; MS (rel. intensity) *m/z* 170 (M^++1, 14.0), 169 (M^+, 55.1), 85 (100), 43 (83).

3-*t*-Butyl-2-oxotetrahydrofurano[3,4-*d*]isoxazoline (3c): colorless oil; ^{1}H NMR δ 1.35 (*s*, 9H), 4.24 (*d*, *J*=9.5 Hz, 1H), 4.46 (*dd*, *J*=2.9 and 10.8 Hz, 1H), 4.61 (*d*, *J*=5.9 and 10.9 Hz, 1H), 5.47 (*ddd*, *J*=2.6, 5.9, and 9.3 Hz, 1H); IR (neat) ν_{max} 1770, 1167 cm^{-1}; MS (rel. intensity) *m/z* 184 (M^++1, 60.9), 183 (M^+, 6.7), 124 (97.3), 99 (22.5), 57 (100).

3-Cyclohexyl-2-oxotetrahydrofurano[3,4-*d*]isoxazoline (3d): mp 88.5-89 ℃; ^{1}H NMR δ 1.26-1.84 (*m*, 8H), 1.92-2.08 (*m*, 2H), 2.59 (*td*, *J*=3.4 and 11.2 Hz, 1H), 4.20 (*d*, *J*=9.7 Hz, 1H), 4.46 (*dd*, *J*=2.4 and 11.0 Hz, 1H), 4.60 (*dd*, *J*=6.0 and 11.0 Hz, 1H), 5.42 (*ddd*, *J*=2.5, 6.0, and 9.7 Hz, 1H); ^{13}C NMR δ 25.80, 29.41, 30.88, 35.45, 54.91, 74.28, 77.00, 80.26, 157.65, 171.05; IR (KBr) ν_{max} 1754, 1169 cm^{-1}; MS (rel. intensity) *m/z* 209 (M^+, 9.4), 180 (25.2), 141 (100), 85 (78.4), 41 (88); Anal. Calcd. for $C_{11}H_{15}NO_3$: C, 63.14; H, 7.23; N, 6.69. Found: C, 63.11; H, 7.32; N, 6.70.

3-Phenyl-2-oxotetrahydrofurano[3,4-*d*]isoxazoline (3e): mp 156-157 ℃ (lit.[14] mp 157-158 ℃); ^{1}H NMR δ 4.64 (*d*, *J*=9.3 Hz, 1H), 4.65 (*dd*, *J*=2.2 and 11.2 Hz, 1H), 4.69 (*dd*, *J*=5.5 and 11.3 Hz, 1H), 5.65 (*ddd*, *J*=2.2, 5.5, and 9.5 Hz, 1H), 7.45-7.47 (*m*, 3H), 7.93-7.95 (*m*, 2H); IR (KBr); ν_{max} 1769, 1205, 1160 cm^{-1}; MS (rel. intensity) *m/z* 203 (M^+, 40.0) 144 (93.4), 128 (39.2), 77 (100), 52 (63.3).

3-(2-Chlorophenyl)-2-oxotetrahydrofurano[3,4-*d*]isoxazoline (3f): mp 74-76 ℃; ^{1}H NMR δ 4.64 (*d*, *J*=2.6 Hz, 1H), 4.65 (*d*, *J*=4.8 Hz, 1H), 5.00 (*d*, *J*=9.6 Hz, 1H), 5.35 (*ddd*, *J*=2.6, 4.7, and 9.6 Hz, 1H), 7.40-7.47 (*m*, 3H), 7.91-7.96 (*m*, 3H); IR (KBr) ν_{max} 1767, 1192 cm^{-1}; MS (rel. intensity) *m/z* 239 (M^++2, 20.0), 237 (M^+, 53.0) 178 (100), 151 (57.3), 128 (43.1), 75 (63.1), 45 (60.3).

3-Octyl-2-oxotetrahydrofurano[3,4-*d*]isoxazoline (3g): mp 60-61.5 ℃; ^{1}H NMR δ 0.88 (*t*, *J*=6.4 Hz, 3H), 1.27 (brs, 11H), 1.54-1.77 (*m*, 2H), 2.37-2.69 (*m*, 2H), 4.14 (*d*, *J*=9.6 Hz, 1H), 4.49 (*dd*, *J*=2.3 and 10.9 Hz, 1H), 4.64 (*dd*, *J*=5.9 and 10.9 Hz, 1H), 5.46 (*ddd*, *J*=2.4, 5.8, and 9.6 Hz, 1H); IR (KBr) ν_{max} 1750, 1168 cm^{-1}; MS (rel. intensity) *m/z* 240 (M^++1, 3.2), 239 (M^+, 6.9) 196 (24.2), 154 (78.0), 141 (100),

122 (26.7), 96 (21.7).

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4-Deoxy-Analogs of *p*-Nitrophenyl β-D-Galactopyranosides for Specificity Study with β-Galactosidase from *Escherichia coli*.

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The synthesis is reported of *p*-nitrophenyl glycosides of D-galactose modified at C-4 with azido- (**5**), amino- (**6**) group and fluorine (**13**). 4-Azido-2,3,6-tri-*O*-benzoyl-4-deoxy-α-D-galactopyranosyl chloride and 2,3,6-tri-*O*-benzoyl-4-deoxy-4-fluoro-α-D-galactopyranosyl bromide were coupled with potassium *p*-nitrophenoxide in the presence of 18-crown-6 giving the corresponding *p*-nitrophenyl 4-azido- and 4-fluoro-4-deoxy-β-D-galactopyranoside derivatives. *p*-Nitrophenyl 4-amino-4-deoxy-β-D-galactopyranoside (**6**) was obtained by selective reduction of *p*-nitrophenyl 4-azido-4-deoxy-β-D-galactopyranoside (**5**) using 1,3-propane dithioltriethylamine. These galactoside analogs were slowly hydrolyzed in the increasing rate order of **5**, **6** and **13** by β-galactosidase from *Escherichia coli*.

Introduction

β-Galactosidase from *Escherichia coli* is a disaccharidase which catalyzes the hydrolysis and transgalactolysis of β-galactopyranosides with overall retention of configuration at the anomeric center.[1~3] Although a great amount of data has been accumulated on β-galactosidase, little is known about the active site.[4,5] The action mechanism of galactosidases has been suggested, in a somewhat analogous way to lysozyme, to involve the formation of a galactosyl-enzyme intermediate by a nucleophile and a general acid catalytic group located at the active site and its subsequent hydrolysis or transglycosidation.[4~10] Efficiency in the formation of a galactosyl-enzyme intermediate relates to substrate's susceptibility to galactosidase *i.e.* satisfaction to a strict glycon specificity is prerequsite for the activity.[8~10]

Amino and fluoro sugars are invaluable analogs[11~20] to assess the role of a sugar OH group as an activity determinant and to elucidate the mechanism of specificity and activity for carbohydrate modifying enzymes. Substrate specificity study using methyl 4-amino- and 4-fluoro-4-deoxy-β-D-galactopyranosides (**7** and **9β**) for β-galactosidase from *Escherichia coli* and their α-anomers for α-galactosidase from *Aspergillus fumigatus* showed that both enzymes have extremely strict specificity for the 4-OH group of D-galactose.[11] The strict glycon specificity of galactosidases was also observed with methyl 5-thio-β-D-galactopyranoside.[11] Those results were contrasting with the relatively loose glycon specificity shown by galactose oxidase.[13]

On the other hand, the activity of β-galactosidase is known