Reaction of Pyrano- and Furo[3,2-*c*]pyridine *N*-Oxides with Trimethylsilyl Cyanide

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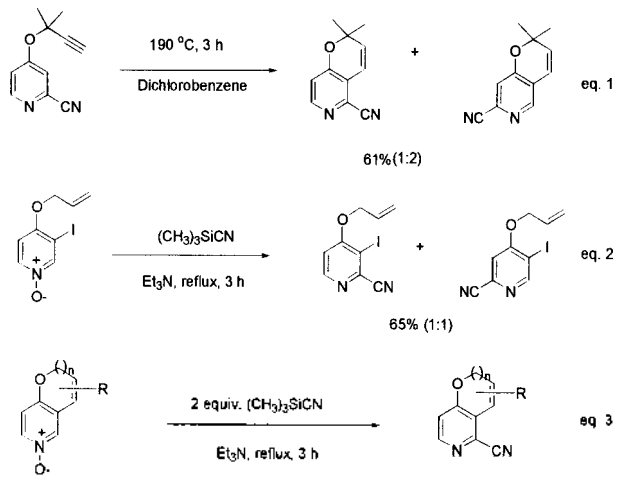
Since the cyanated heterocycles can be transformed to the corresponding carboxamides, carboxylic acids, and esters.[1] The regioselective cyanation of heterocycles is very important to find pharmaceutical agents. Recently, there are many reports for the regioselective cyanation of various heterocycles such as pyridine,[2-4] pyrazole,[5,6] pyrimidine,[7] and imidazole.[8] The general cyanation methods use organo or inorganic cyanide with pyridine quaternary derivatives.[9,10] However, only two papers reported cyanation to fused heterocycles.[11,12]

We have been interested in regioselective cyanation of various fused heterocycles to synthesize pharmaceutically interesting compounds. To obtain selectively cyanated pyranopyridines, we examined thermal [3,3]-sigmatropic rearrangement according to known procedure (eq. 1).[13] We also examined the cyanation of 3-iodo-4-allyloxypyridines *N*-oxide to prepare 4-allyl-2-cyano-3-iodopyridine (eq. 2). The cyanated 4-allyl-3-iodopyridines is a useful intermediate to synthesize cyanated furopyridines using palladium-catalyzed cyclization.[14] However, any regioseletively cyanated heterocycles could not be obtained by the above procedures.

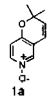
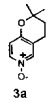
To overcome above discouraging results, we examined the regioselective cyanation to variously substituted pyranopyridine and furopyridine *N*-oxide derivatives with trimethylsilyl cyanide and Et_3N as a solvent (eq. 3). The cyanation results of pyrano- and furo[3,2-*c*]pyridine *N*-oxides are summarized in Table 1. It was proposed that the reaction took place via *O*-silylation, addition of cyanide, and elimination of trimethylsilanol.[3] The starting pyrano- and furo[3,2-*c*]pyridine *N*-oxide derivatives were prepared by known procedures.[1,13,14] The cyanation of **1a** provided **1b** as a major product in an isomeric ratio of 9 : 1 (**1b** : **1c**).



The ratio of isomers were easily determined by ^{1}H NMR spectra and HPLC. The ^{1}H NMR of **1b** showed two doublet proton of pyridine moiety. On the other hand, the ^{1}H NMR of **1c** showed two singlet proton of pyridine moiety. Surprisingly, only **2b** was obtained from the cyanation of **2a**. The cyanation of **3a** and **4a** were also examined in order to know the scope of selectivity. The reactions provided predominantly 5-cyanopyrano[3,2-*c*]pyridine derivatives in moderate yields. On the other hand, the cyanation of **5a** gave **5b** and **5c** in an isomeric ratio of 1 : 1. The regioseletive cyanation to pyrano[3,2-*c*] pyridine *N*-oxide derivatives depend on the substitutent of pyrano[3,2-*c*] pyridine.

Further, we examined the regioseletive cyanation of various 3-substituted furo[3,2-*c*]pyridine *N*-oxides. The cyanation of **6a** provided **6b** with complete regioseletivity in 60-65% isolated yield. Finally, the cyanation of **7a** provided 1 : 1

Table 1. Regioseletive cyanation of Pyrano-and Furo[3,2-*c*]pyridine *N*-oxide Derivatives

Entry[a]	Starting Material	Products	Isolation Yield (%)	Isomeric Ratio
1	 1a	 1b  1c	61	(1b:1c = 9:1)[b]
2	 2a	 2b	65	
3	 3a	 3b	64	
4	 4a	 4b  4c	55	(4b:4c = 97:3)[b]
5	 5a	 5b  5c	75	(5b:5c = 1:1)[c]
6	 6a	 6b	62(R_1=CH_3) 65(R_1=C_2H_5) 63(R_1=$CH(CH_3)_2$)	
7	 7a	 7b  7c	50	(7b:7c = 1:1)[c]

[a] The reaction used 2.0 equiv. of trimetylsilyl cyanide, and Et_3N as a solvent at 100 °C. [b] The isomeric ratio was determined by ^{1}H NMR and HPLC. [c] The isomeric ratio was determined by silicagel column chromatograpy.

(**7b**:**7c**) isomeric products. The aromaticity of furo[3,2-*c*] pyridine is more important compared to steric effect for the selective cyanation of furo[3,2-*c*]pyridine *N*-oxide.

In summary, the cyanation of pyrano- and furo[3,2-*c*] pyridine *N*-oxides provide regioseletively cyanated fused pyridine derivatives. The compounds could be very useful intermediates for the synthesis of biologically active compounds. We will further examine the regioseletive cyanation to various heterocyclic *N*-oxides.

Experimental Sections

The ^{1}H NMR spectra were obtained on a Varian Gemini 200 MHz NMR Spectrometer. The GC-MS spectral were obtained on a Shimazu QP 1000 mass spectrometer. Melting points were deterimined on MUl-TEM apparatus and were uncorrected. All chemicals were used directly as obtained from commerical sources unless otherwise noted.

General procedure for pyrano- or furo[3,2-c]pyridine *N*-oxides. A mixture of pyrano- or furo[3,2-*c*]pyridine (5 mmol) and *m*-chloroperbenzoic acid (1.72 g, purity 50-75%, 5-7 mmol) in dichloromethane was stirred at room temperature for 20 hours. The mixture was filtered through glass filter. The dichloromethane layer was dried over anhydrous $MgSO_4$ and concentrated. The corresponding *N*-oxide was obtained in 60-80% isolated yield after silicagel column chromatography (hexane : ethyl acetate : methanol = 4 : 4 : 1).

General procedure for cyanation of pyrano- or furo [3,2-c]pyridine *N*-oxide. A pyrano- or furo[3,2-*c*]pyridine *N*-oxide (1 mmol) and trimethylsilyl cyanide (2 mmol) were dissolved in Et_3N (2 mL). The reaction mixture was stirred at refluxing temperature for 3-4 hours. The mixture was poured into 20 mL of cold water. The product was extracted with two 20 mL portions of ethyl acetate. The ethyl acetate layer was dried over anhydrous $MgSO_4$ and concentrated. The corresponding cyanated compound was obtained after silica gel column chromatography.

The following cyanated compounds (**1b-7c**) were obtained using above general procedure.

5-Cyano-2,2-dimethyl-2*H*-pyrano[3,2-c]pyridine (1b). Yellow oil; yield 55%; ^{1}H NMR ($CDCl_3$) δ 8.27 (d, 1H, J = 5.5 Hz, ArH), 6.86 (d, 1H, J = 5.5 Hz, ArH), 6.66 (d, 1H, J = 10.0 Hz, vinylic), 5.94 (d, 1H, J = 10.0 Hz, vinylic), 1.52 (s, 6H, CH_3); Mass *m/e* (%) 168 (100), 188 (20, M^+).

7-Cyano-2,2-dimethyl-2*H*-pyrano[3,2-c]pyridine (1c). Semi-solid; yield 6%; ^{1}H NMR ($CDCl_3$) δ 8.20 (s, 1H, ArH), 7.06 (s, 1H, ArH), 6.39 (d, 1H, J = 10.0 Hz, vinylic), 5.84 (d, 1H, J = 10.0 Hz, vinylic), 1.50 (s, 6H, CH_3); Mass *m/e* (%) 166 (66), 168 (100), 188 (21, M^+).

5-Cyano-4-methylene-3,4-dihydro-2*H*-pyrano[3,2-c]pyridine (2b). Yellow oil; yield 65%; mp 68-70 °C; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, 1H, J = 5.4 Hz, ArH), 6.93 (d, 1H, J = 5.4 Hz, ArH), 6.27 (s, 1H, vinylic), 5.45 (s, 1H, vinylic), 4.41 (t, 2H, J = 5.8 Hz, OCH_2), 2.70 (t, 2H, J = 5.8 Hz, CH_2); Mass *m/e* (%) 168 (100), 188 (17, M^+).

5-Cyano-2,2-dimethyl-3,4-dihydro-2*H*-pyrano[3,2-c]pyridine (3b). Yellow oil; yield 64%; ^{1}H NMR ($CDCl_3$) δ 8.31 (d, 1H, J = 5.5 Hz, ArH), 6.95 (d, 1H, J = 5.5 Hz, ArH), 2.13 (t, 2H, J = 5.8 Hz, CH_2), 1.83 (t, 2H, J = 5.8 Hz, CH_2); Mass *m/e* (%) 168 (100), 188 (25, M^+).

5-Cyano-4-methyl-3,4-dihydro-2*H*-pyrano[3,2-c] pyridine (4b). Yellow oil; yield 54%; mp 65-67 °C; ^{1}H NMR ($CDCl_3$) δ 8.37 (d, 1H, J = 5.6 Hz, ArH), 7.08 (d, 1H, J = 5.6 Hz, ArH), 1.38 (d, 3H, J = 7.0 Hz, CH_3); Mass *m/e* (%) 86 (100), 174 (23, M^+).

7-Cyano-4-methyl-3,4-dihydro-2*H*-pyrano[3,2-c] pyridine (4c). Semi-solid; yield 1%; ^{1}H NMR ($CDCl_3$) δ 8.27 (d, 1H, J = 5.6 Hz, ArH), 6.88 (d, 1H, J = 5.6 Hz, ArH), 4.32 (m, 2H, OCH_2), 3.30 (m, 1H, CH), 2.13 (m, 1H, CH), 1.82 (m, 1H, CH), 1.43 (d, 3H, J = 7.0 Hz, CH_3); Mass *m/e* (%) 159 (100), 174 (20, M^+).

5-Cyano-4,4-dimethyl-3,4-dihydro-2*H*-pyrano[3, 2-c]pyridine (5b). mp 48-50 °C; yield 37%; ^{1}H NMR ($CDCl_3$) δ 8.22 (d, 1H, J = 6.6 Hz, ArH), 6.90 (d, 1H, J = 6.6 Hz, ArH), 4.23 (t, 2H, J = 5.4 Hz, OCH_2), 1.95 (t, 2H, J = 5.4 Hz, CH_2), 1.60 (s, 6H, CH_3); Mass *m/e* (%) 173 (100), 188 (17, M^+), 189 (40, M^++1).

7-Cyano-4,4-dimethyl-3,4-dihydro-2*H*-pyrano[3, 2-c]pyridine(5c). mp 162-163 °C; yield 37%; ^{1}H NMR ($CDCl_3$) δ 8.45 (s, 1H, ArH), 7.05 (s, 1H, ArH), 4.23 (t, 2H, J = 5.4 Hz, OCH_2), 1.95 (t, 2H, J = 5.4 Hz, CH_2), 1.60 (s, 6H, CH_3); Mass *m/e* (%) 173 (100), 188 (16, M^+), 189 (29, M^++1).

4-Cyano-3-methylfuro[3,2-c]pyridine (6b, $R_1 = CH_3$).[14] mp 120-122 °C; yield 62%; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, 1H, J = 5.6 Hz, ArH), 7.60 (d, 1H, J = 5.6 Hz, ArH), 7.55 (s, 1H, ArH), 2.50 (s, 3H, CH_3); Mass *m/e* (%) 130 (23.7), 158 (100, M^+).

4-Cyano-3-ethylfuro[3,2-c]pyridine (6b, $R_1 = C_2H_5$). mp 73-75 °C; yield 65%; ^{1}H NMR ($CDCl_3$) δ 8.60 (d, 1H, J = 5.4 Hz, ArH), 7.61 (d, 1H, J = 5.4 Hz, ArH), 7.59 (s, 1H, ArH), 3.00 (q, 2H, J = 6.0 Hz, CH_2), 1.45 (t, 3H, J = 6.0 Hz, CH_3); Mass *m/e* (%) 172 (100, M^+).

4-Cyano-3-isopropylfuro[3,2-c]pyridine (6b, $R_1 = CH(CH_3)_2$). Semi-solid; yield 63%; ^{1}H NMR ($CDCl_3$) δ 8.50 (d, 1H, J = 5.4 Hz, ArH), 7.60 (s, 1H, ArH) 7.58 (d, 1H, J = 5.4 Hz, ArH), 3.40 (m, 1H, CH), 1.35 (d, 6H, J = 5.8 Hz, CH_3); Mass *m/e* (%) 186 (100, M^+).

4-Cyano-3,3-dimethyl-2,3-dihydrofuro[3,2-c] pyridine (7b). Semi-solid; yield 25%; ^{1}H NMR ($CDCl_3$) δ 8.36 (d, 1H, J = 5.4 Hz, ArH), 6.90 (d, 1H, J = 5.4 Hz, ArH), 4.45 (s, 2H, OCH_2), 1.50 (s, 6H, CH_3); Mass *m/e* (%) 159 (100), 174 (23, M^+).

6-Cyano-3,3-dimethyl-2,3-dihydrofuro[3,2-c] pyridine (7c). mp 120-125 °C; yield 25%; ^{1}H NMR ($CDCl_3$) δ 8.30 (s, 1H, ArH), 7.10 (s, 1H, ArH), 4.35 (s, 2H, OCH_2), 1.45 (s, 6H, CH_3); Mass *m/e* (%) 159 (100), 174 (20, M^+).

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Synthesis and Cytotoxicity of (−)-(4*R*,5*R*)-5-*C*-(11-Methoxy)muricatacin

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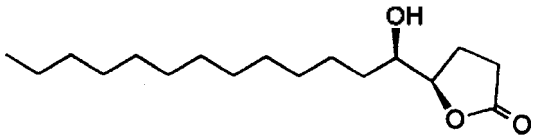
Muricatacin (1), an acetogenin derivative, which is isolated from the seeds of the tropical fruit *Annona muricata* L., has received a great deal of attention because it shows some cytotoxicities against human tumor cell lines and its congeners show a wide range of biological activities.[1] The natural muricatacin is comprised of (−)-(4*R*,5*R*)-5-hydroxyheptadeca-4-nolide and its (+)-(4*S*,5*S*) enantiomer, with the former predominating. (+)-Muricatacin and/or (−)-muricatacin was recently synthesized from various starting materials.[2]

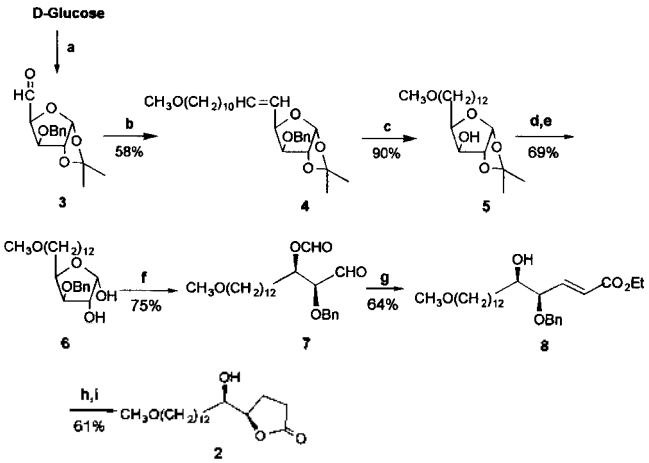


(-)-(4*R*,5*R*)-Muricatacin (1)

In connection with our projects to understand structure-activity relationship (SAR) of acetogenin derivatives, we recently reported that the stereochemistry at C_4 and C_5 position of muricatacin did not significantly affect the cytotoxicities.[3] In the continuous effort to obtain SAR, we were interested in evaluating the effect of the long alkyl chain in muricatacin on cytotoxicity. Thus, we substituted the hydrophobic methyl group in the long alkyl chain with the more hydrophilic methoxy group. Here, we report a stereocontrolled synthesis of pure (−)-(4*R*,5*R*)-5-*C*-(11-methoxy) muricatacin (2) **from D-glucose, as well as its cytotoxicity.**

Results and Discussion

Synthesis. According to Scheme 1, the synthesis of (-)-(4*R*,5*R*)-5-*C*-(11-methoxy)muricatacin (2), (or (-)-(4*R*,5*R*)-5-(11-methoxy)-hydroxy-4-heptadecanolide) was started from 3-*O*-benzyl-1,2-*O*-isopropylidene-α-D-xylo-pentoaldo-1,4-furanose (3) which was easily prepared from D-glucose in four steps.[4-7] Wittig reaction of 3 with n-BuLi and 11-methoxy-undecanyltriphenylphosphonium bromide (3a) gave a 3-*O*-benzyl-5,6-dideoxy-5-C-(11-methoxy)-undecyl-1,2-isopropylidene-α-D-xylo-dode-5-cenofuranose (4), which was hydrogenated in the presence of 10% Pd-C under 1 atm of hydrogen to give a 5,6-dideoxy-1,2-isopropylidene-5-C-(11-methoxy-n-undecanyl)-α-D-glucofuranose (5). Monoprotection of the hydroxy group at 3-position in 5 with benzyl chloride in tetrahydrofuran (THF) using NaH as a base followed by removal of the isopropylidene group with 9.6 N HCl afforded 1,2-diol compound 6. After (2*S*,3*R*)-*O*-protected 2,3-dihydroxy aldehyde 7 was obtained from the oxidative cleavage of 6 with sodium periodate, it was



Scheme 1. a) See reference 8; b) 9.6 N n-BuLi, 11-methoxy-undecanyl-triphenylphosphonium bromide (3a), THF, -78 °C - rt ; c) H_2, Pd-C, EtOAc, d) NaH, BnCl, THF, rt, 5h; e) 9.6 N HCl/TFA, DME, rt, 48 h; f) $NaIO_4$, MeOH, rt, 1 h; g) NaH, $(EtO)_2$-$POCH_2CO_2Et$, THF, rt, 3 h; h) H_2, Pd-C, EtOAc, rt, 24 h; i) TFA-H_2O (4:1), rt, 3 h.