A Convenient Method for *C*-Azanucleosides Synthesis

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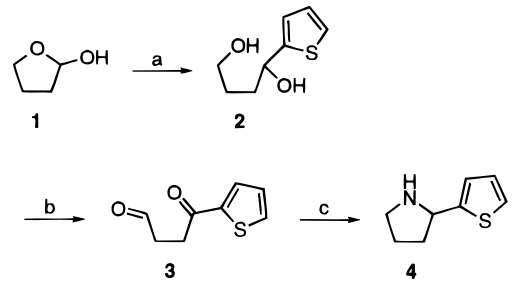
Introduction

As a part of our program for synthesis and evaluation of the *C*-nucleosides as a new type of DNA unit,[1] we have been interested in the *C*-azanucleosides in which the endocyclic ribosyl ring oxygen is replaced with a nitrogen atom. To our knowledge, many modified nojirimycins, which function as effective glycosidase inhibitors, have been reported,[2] and only three *C*-azanucleosides[3] have been synthesized as nojirimycin analogs. However, their preparative methods remain limited and their characteristic properties are not widely known: 2α,3α-dihydroxy-4*β*-(hydroxymethyl)-*N*-carbomethoxypyrrolidine as a showdomycin analogue starting from teloidinone,[3a] as well as 1,4-dideoxy-1,4-imino-1(*S*)-phenyl-D-ribitol and 1,4-dideoxy-1,4-imino-1(*S*)-(4-imidazolyl)-D-ribitol as a new class of *N*-glycohydrolase transition state analog inhibitors.[3b] Therefore, we wish herein to present a general and useful method for the synthesis of *β*-*C*-azanucleosides.

Results

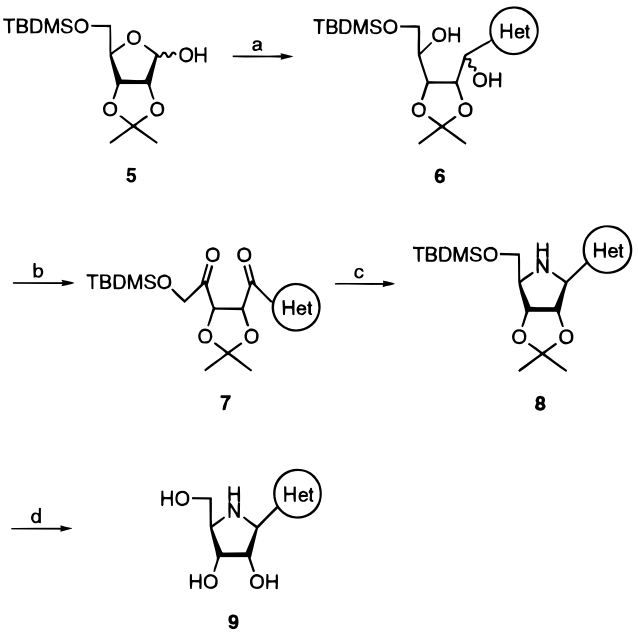
As a model experiment, 2-pyrrolidinylthiophene (**4**)[4] was synthesized starting from 2-hydroxytetrahydrofuran *via* a sequential procedure of the addition of 2-thienyllithium (**2**: 80% yield), the Swern oxidation (**3**: 60% yield), and reductive aminocyclization using ammonium formate and $NaBH_3CN$ (**4**: 32% yield).[5] The reaction procedure is shown in Scheme 1.

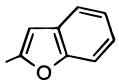
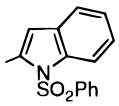
Scheme 1[a]



[a] Reagents and conditions: (a) 2-Thienyllithium, THF, rt, 1.5 h; (b) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C, 3 h; (c) HCO_2NH_4, $NaBH_3CN$, MeOH, rt, 4 h.

Scheme 2[a]



Het	Yield (%)			
	6	**7**	**8**	**9**
	94	80	34	94
	87	88	39	75
	71	86	56	98

[a] Reagents and conditions: (a) 2-Aryllithium, THF, rt, 1 h; (b) DMSO, TFAA, Et_3N, CH_2Cl_2, −78 °C to rt, 4 h; (c) HCO_2NH_4, $NaBH_3CN$, MeOH, rt, 18 h; (d) 70% CF_3CO_2H, 50 °C, 2 h.

Next, the desired *β*-*C*-azanucleosides **9** were synthesized by the same way as the model experiment (Scheme 2) [**5** → **6**; step a]: A THF solution containing the lithium salt of a heterocycle was added to 5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribofuranose (**5**)[6] which

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(2) (a) Hashimoto, H.; Hayakawa, M. *Chem. Lett.* **1989**, 1881. (b) Legler, G. *Adv. Chem. Biochem.* **1990**, *48*, 318. (c) Poitout, L.; Merrer, Y. L.; Depezay, J.-C. *Tetrahedron lett.* **1994**, *35*, 3293. (d) Fowler, P. A.; Haines, A. H.; Taylor, R. J. K.; Chrystal, E. J. T.; Gravestock, M. B. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2229. (e) Martin, O. R.; Saavedra, O. M. *Tetrahedron Lett.* **1995**, *36*, 799. (f) Ichikawa, M.; Igarashi, Y.; Ichikawa, Y. *Tetrahedron Lett.* **1995**, *36*, 1767. (g) Wong, C.-H.; Provencher, L.; Porco, J. A., Jr.; Jung, S.-H.; Wang, Y.-F.; Chen, L.; Wang, R.; Steensma, D. H. *J. Org. Chem.* **1995**, *60*, 1492. (h) Hiranuma, S.; Shimizu, T.; Nakata, T.; Kajimoto, T.; Wong, C.-H. *Tetrahedron Lett.* **1995**, *36*, 8247. General synthetic method consists of (1) aldolase reaction to the azido keto sugar and (2) Pd/C-mediated reductive amination: Look, G. C.; Fotsch, C. H.; Wong, C.-H. *Acc. Chem. Res.* **1993**, *26*, 182 and references cited.

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(4) (a) Burckhalter, J. H.; Short, J. H. *J. Org. Chem.* **1958**, *23*, 1281. (b) McGhie, J. F.; Ross, W. A.; Laney, D. H. *J. Chem. Soc.* **1962**, 2578.

(5) Martin, O. R.; Saavedra, O. M. *Tetrahedron Lett.* **1995**, *36*, 799.

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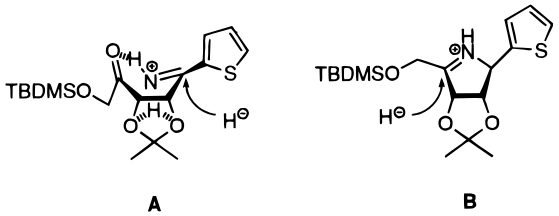
S0022-3263(96)00523-3 CCC: $12.00

Scheme 3



A **B**

was prepared by the usual way [(1) small amount of H_2SO_4/acetone; (2) *tert*-butylchlorodimethylsilane (TBDMSCl), imidazole/CH_2Cl_2]. After being stirred for 1 h at 0 °C, the reaction mixture was purified by column chromatography to give aryl ribitols **6** [**6** → **7**; step b]: **6** was oxidized with DMSO, trifluoroacetic anhydride (TFAA), and Et_3N and then purified by column chromatography to give aryl diketones **7** [**7** → **8**; step c]: A mixture of $NaBH_3CN$, HCO_2NH_4, and molecular sieves (3A) was added to the methanol solution containing **7**. After stirring for 18 h at room temperature, the reaction mixture was purified by preparative TLC on silica gel to give aza sugars **8** [**8** → **9**; step d]: Then **8** was treated with 70% trifluoroacetic acid for 2 h at 50 °C to give the desired *β*-*C*-azanucleosides **9** in good yields.

The stereochemistry of **8** was determined mainly by the result of NOESY in NMR measurements (1-H ↔ 4-H). Further, the *β*-stucture was supported from ^{1}H-NMR data on the basis of chemical shifts values and their difference[7] of the two methyl groups of the isopropylidene moiety. These values of **8a** (δ 1.30 and 1.53 ppm; $\Delta\delta$ = 0.23 ppm) were very similar to those of 2-(2′,3′-*O*-isopropylidene-*β*-ribofuranosyl)furan (δ 1.37 and 1.59; $\Delta\delta$ = 0.22).[8] The structure determination for **6**, **7**, and **9** was carried out by ^{1}H-NMR and mass (FAB) measurements together with elemental analysis.

The *β*-stereoselectivity of **8** may appear by the following process: (1) stereoselective amination of the 1-carbonyl group to give the 1(*R*)-amino group (intermediate **A**); (2) nucleophilic attack of the 1-amino group to 4-carbonyl group; (3) dehydration to an imino sugar; (4) *si*-plane attack of hydride ion to C-4 of iminosugar perhaps due to the steric hindrance (intermediate **B**). The appearance of this selectivity cannot be explained fully. However, the predominant *β*-selectivity has also been reported in the preparation of pyrrolidine aminosugars.[9]

In conclusion, the present method consists of the *β*-stereoselective synthesis of *C*-azanucleosides, which makes possible the synthesis of various kinds of *β*-*C*-azanucleosides easily. The *C*-azanucleosides obtained by this method are now under study for their chemical properties and for the evaluation of their biological activity.

Experimental Section

All reactions were conducted in oven-dried (120 °C) glassware under dry argon. Ether and THF were distilled from sodium benzophenone ketyl. Pyridine was distilled from CaH_2. Microanalyses were performed at the Chemical Analysis Center of Chiba University. ^{1}H NMR spectra were recorded on a 270 MHz, a 400 MHz, or a 500 MHz spectrometer. ^{13}C NMR spectra were recorded on a 126 MHz spectrometer. Mass spectra were recorded using the FAB or an EI methods. Purification was carried out by column chromatography and preparative TLC (pTLC).

Lithiation of Aromatic Heterocycles (thiophene, benzofuran). To a solution of aromatic heterocycle (1.5 mmol) in THF (5 mL) was added *n*-buthyllithium (1.0 equiv, 1.6 M hexane solution) dropwise at 0 °C. The solution was allowed to rise to room temperature and stirred for 1 h.

Lithiation of *N*-(Phenylsulfonyl)indole. To a solution of *N*-(phenylsulfonyl)indole (1.1 g, 4 mmol) in THF (5 mL) was added *n*-buthyllithium (1.0 equiv, 1.6 M hexane solution) dropwise at 0 °C. The solution was stirred at the same temperature for 1 h.

Preparation of 1-(2′-Thienyl)-1,4-butanediol (2). To a solution of 2-hydroxytetrahydrofuran (**1**)[10] (88 mg, 1 mmol) in THF (5 mL) was added dropwise thienyllithium in THF solution (3.5 equiv) at 0 °C under stirring. After stirring at room temperature for 1.5 h, the reaction mixture was quenched with H_2O, diluted with $CHCl_3$, and then purified by pTLC (AcOEt/hexane, 1/1) to give **2** as colorless crystals in 88% yield: IR (KBr) 1440, 1480, 2850, 2900, 3060, 3150−3300 cm^{-1}; HRMS (FAB, NBA + KI) calcd for $C_8H_{12}O_2SK$ *m*/*e* (M + K) 211.0195, found 211.0182; ^{1}H NMR (270 MHz, $CDCl_3$) δ 1.70 (2H, m, 3-CH_2), 1.90 (2H, m, 2-CH_2), 3.70 (2H, m, 4-CH_2), 4.90 (1H, t, 1-CH, $J_{1,2}$ = 3 Hz), 6.90−7.30 (3H, m, thiophene). Anal. Calcd for $C_8H_{12}O_2S$: C, 55.78; H, 7.02. Found: C, 55.60; H, 6.88.

Preparation of 1-(2′-Thienyl)-1,4-dioxobutane (3). A mixture of DMSO (0.28 mL, 4 mmol), TFAA (0.6 mL, 4 mmol), and CH_2Cl_2 (4 mL) was stirred at −78 °C for 1 h. To the mixture obtained above was added 4 mL of CH_2Cl_2 solution containing **2** (173 mg, 1 mmol) at −78 °C. After the resultant mixture was stirred at the same temperature for 2 h, Et_3N (1.2 mL, 8 mmol) was added and the resultant mixture was stirred at −78 °C for 0.5 h and then at room temperature for 0.5 h. After quenching with H_2O, extracting with $CHCl_3$, washing the organic phase with 1 N HCl, and neutralizing with $NaHCO_3$, purification was performed by pTLC (AcOEt/hexane, 1/1) to give **3** as a yellow oil in 71% yield: IR (neat) 1408, 1560, 1660, 1720, 2800, 2880, 3050 cm^{-1}; MS (EI) *m*/*e* 168 (M); ^{1}H NMR (270 MHz, $CDCl_3$) δ 2.90 (2H, m, 3-CH_2), 3.20 (2H, t, 2-CH_2, $J_{2,3}$ = 6 Hz), 7.10−7.70 (3H, m, thiophene), 9.90 (1H, t, 4-CH, $J_{3,4}$ < 0.5 Hz). Anal. Calcd for $C_8H_8O_2S$: C, 57.12; H, 4.79. Found: C, 57.33; H, 4.64.

2-(2-Pyrrolydinyl)thiophene (4). To a mixture of $NaBH_3CN$ (132 mg, 2.1 mmol), HCO_2NH_4 (132 mg, 2.1 mmol), and molecular sieves (3A) (500 mg) was added a MeOH solution (20 mL) containing **3** (117 mg, 0.7 mmol) at room temperature for 24 h. After being filtered through Celite and extracted with $CHCl_3$, the mixture was purified by pTLC ($CHCl_3$/MeOH, 12/1) to give **4**[11] as a yellow oil in 32% yield.

Preparation of Aryl Ribitols 6. Typical Procedure. The organolithium reagent of aromatic heterocycle (THF solution, 4 mmol) was added dropwise to a solution of **5** (304 mg, 1 mmol) in THF (10 mL) at 0 °C and stirred at room temperature for 1 h. The mixture was quenched with H_2O, diluted with $CHCl_3$, dried over Na_2SO_4 and concentrated. The residue was purified by column chromatography (AcOEt/hexane, 1/3) to give **6**.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-1-(2-thienyl)-D-ribitol (6a): oil; IR (neat) 840, 1070, 1250, 2900, 3450 cm^{-1}; HRMS (FAB, NBA + KI) calcd for $C_{18}H_{32}O_5SSiK$ *m*/*e* (M + K) 427.1377, found 427.1375; ^{1}H NMR (270 MHz, $CDCl_3$): **(*R*-form)** δ 0.09 (6H, s, TBDMS Si-Me), 0.93 (9H, s, TBDMS Si-^{t}Bu), 1.31 (3H, s, isopropylidene-CH_3), 1.40 (3H, s, isopropylidene-CH_3), 3.43 (1H, bs, 1 or 4-OH), 3.68−4.51 (5H, m, 2-H, 3-H, 4-H, 5-Ha, 5-Hb), 4.80 (1H, bs, 1 or 4-OH), 5.13 (1H, m, 1-H), 6.96−7.29 (3H, m, thiophene); **(*S*-form)** δ 0.12 (6H, s, TBDMS Si-Me), 0.91 (9H, s, TBDMS Si-^{t}Bu), 1.38 (3H, s, isopropylidene-CH_3), 1.54 (3H, s, isopropylidene-CH_3), 2.75 (1H, bs, 1 or 4-OH), 3.13 (1H, bs, 1- or 4-OH), 3.68−4.51 (5H, m, 2-H, 3-H, 4-H, 5-Ha, 5-Hb), 5.40 (1H, m, 1-H), 6.96−7.29 (3H, m, thiophene). Anal. Calcd for $C_{18}H_{32}O_5SSi$: C, 55.63; H, 8.30. Found: C, 55.77; H, 8.18.

1-(2-Benzofuryl)-5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-D-ribitol (6b): oil; IR (neat) 840, 1090, 1250, 1440, 2900, 3350 cm^{-1}; HRMS (FAB, NBA + KI) calcd for $C_{22}H_{34}O_6$-

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SiK *m/e* (M + K) 461.1762, found 461.1757; ^{1}H NMR (270 MHz, $CDCl_3$): **(*R*-form)** δ 0.12 (6H, s, TBDMS Si-Me), 0.92 (9H, s, TBDMS Si-^{t}Bu), 1.31 (3H, s, isopropylidene-CH_3), 1.38 (3H, s, isopropylidene-CH_3), 3.45 (1H, bs, 1 or 4-OH), 3.72 (1H, m, 5-Ha), 3.94 (1H, m, 5-Hb), 4.15 (1H, m, 4-H), 4.21 (1H, m, 3-H), 4.72 (1H, bs, 1 or 4-OH), 5.06 (1H, m, 1-H), 6.72 (1H, s, benzofuran 3′-H), 7.19−7.28 (2H, m, benzofuran 5′-H, 6′-H), 7.48−7.62 (2H, m, benzofuran 4′-H, 7′-H). Anal. Calcd for $C_{22}H_{34}O_6Si$: C, 62.53; H, 8.11. Found: C, 62.63; H, 8.22.

5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-1-[2-[*N*-(phenylsulfonyl)indolyl]]-D-ribitol (6c): foam; IR (KBr) 870, 1090, 1200, 1400, 1470, 2900, 3400 cm^{-1}; HRMS (FAB, NBA + KI) calcd for $C_{28}H_{39}O_7NSSiK$ *m/e* (M + K) 600.1854, found 600.1854; ^{1}H NMR (270 MHz, $CDCl_3$): **(*R*-form)** δ 0.11 (6H, s, TBDMS Si-Me), 0.93 (9H, s, TBDMS Si-^{t}Bu), 1.37 (3H, s, isopropylidene-CH_3), 1.53 (3H, s, isopropylidene-CH_3), 2.85 (1H, bs, 1 or 4-OH), 3.29 (1H, bs, 1 or 4-OH), 3.68−4.71 (5H, m, 2-H, 3-H, 4-H, 5-Ha, 5-Hb), 5.98 (1H, m, 1-H), 6.83 (1H, s, indole 3′-H), 7.18−8.16 (9H, m, Ph-H, indole 4′-H, 5′-H, 6′-H, 7′-H); **(*S*-form)** δ 0.13 (6H, s, TBDMS Si-Me), 0.94 (9H, s, TBDMS Si-^{t}Bu), 1.31 (3H, s, isopropylidene-CH_3), 1.38 (3H, s, isopropylidene-CH_3), 3.54 (1H, bs, 1 or 4-OH), 3.68−4.71 (5H, m, 2-H, 3-H, 4-H, 5-Ha, 5-Hb), 4.79 (1H, bs, 1 or 4-OH), 5.80 (1H, m, 1-H), 6.82 (1H, s, indole 3′-H), 7.18-8.16 (9H, m, Ph-H, indole 4′-H, 5′-H, 6′-H, 7′-H). Anal. Calcd for $C_{28}H_{39}O_7NSSi$: C, 59.86; H, 7.00; N, 2.49. Found: C, 59.93; H, 7.09; N, 2.65.

Oxidation of 6 To Give Aryl Diketones 7. Typical Procedure. A solution of TFAA (5 mmol) in CH_2Cl_2 (1 mL) was added dropwise to a solution of DMSO (5 mmol) in CH_2Cl_2 (5 mL) at −78 °C and stirred for 1 h at the same temperature. To the stirring mixture was added dropwise a solution of **6** (1 mmol) in CH_2Cl_2 (3 mL) at −78 °C, and then the reaction mixture was stirred for an additional 2 h at the same temperature. A solution of Et_3N (8 mmol) in CH_2Cl_2 (2 mL) was added dropwise, and the stirring was continued for 0.5 h at −78 °C. The reaction mixture was removed from the cooling bath and allowed to warm to 0 °C with stirring. The reaction mixture was partitioned between CH_2Cl_2 and ice−water. The organic layer was separated, washed with 2 N HCl and saturated aqueous $NaHCO_3$, and dried over Na_2SO_4. The solvent was removed, and the residue was purified by column chromatography (AcOEt/hexane, 1/3) to give **7**.

(2*R*,3*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-1-(2-thienyl)-1,4-pentanedione (7a): oil; IR (neat) 840, 1100, 1240, 1400, 1650, 1720, 2900 cm^{-1}; HRMS (FAB, NBA) calcd for $C_{18}H_{29}O_5SSi$ *m/e* (M + H) 385.1505, found 385.1505; ^{1}H NMR (400 MHz, $CDCl_3$) δ −0.01 (3H, s, TBDMS Si-Me), 0.06 (3H, s, TBDMS Si-Me), 0.85 (9H, s, TBDMS Si-^{t}Bu), 1.46 (3H, s, isopropylidene-CH_3), 1.48 (3H, s, isopropylidene-CH_3), 4.34 (1H, d, 5-Ha, J_{gem} = 17.5 Hz), 4.53 (1H, d, 5-Hb, J_{gem} = 17.5 Hz), 4.92 (1H, d, 3-H, $J_{2,3}$ = 6.6 Hz), 5.57 (1H, d, 2-H, $J_{2,3}$ = 6.6 Hz), 7.16 (1H, m, thiophene 4′-H), 7.71 (1H, m, thiophene 3′-H), 7.98 (1H, m, thiophene 5′-H). Anal. Calcd for $C_{18}H_{29}O_5SSi$: C, 56.07; H, 7.58. Found: C, 55.98; H, 7.42.

(2*R*,3*S*)-1-(2-Benzofuryl)-5-*O*-(*tert*-butyldimethylsilyl)-2,3-*O*-isopropylidene-1,4-pentanedione (7b): oil; IR (neat) 870, 1270, 1550, 1690, 1740, 2900 cm^{-1}; HRMS (FAB, NBA) calcd for $C_{22}H_{31}O_6Si$ *m/e* (M + H) 419.1890, found 419.1883; ^{1}H NMR (270 MHz, $CDCl_3$) δ −0.01(3H, s, TBDMS Si-Me), 0.07 (3H, s, TBDMS Si-Me), 0.86 (9H, s, TBDMS Si-^{t}Bu), 1.51 (6H, s, isopropylidene-CH_3), 4.41 (1H, d, 5-Ha, J_{gem} = 17.8 Hz), 4.57 (1H, d, 5-Hb, J_{gem} = 17.8 Hz), 5.02 (1H, d, 3-H, $J_{2,3}$ = 6.7 Hz), 5.67 (1H, d, 2-H, $J_{2,3}$ = 6.7 Hz), 7.31−7.80 (1H, m, benzofuran). Anal. Calcd for $C_{22}H_{31}O_6Si$: C, 62.98; H, 7.45. Found: C, 62.95; H, 7.60.

(2*R*,3*S*)-5-*O*-(*tert*-Butyldimethylsilyl)-2,3-*O*-isopropylidene-1-[2-[*N*-(phenylsulfonyl)indolyl]]-1,4-pentanedione (7c): foam; IR (KBr) 830, 1180, 1250, 1370, 1420, 1680, 1720, 2900 cm^{-1}; HRMS (FAB, NBA + KI) calcd for $C_{28}H_{35}O_7NSSiK$ *m/e* (M + K) 596.1541, found 596.1534; ^{1}H NMR (270 MHz, $CDCl_3$) δ 0.05 (3H, s, TBDMS Si-Me), 0.08 (3H, s, TBDMS Si-Me), 0.90 (9H, s, TBDMS Si-^{t}Bu), 1.34 (3H, s, isopropylidene-CH_3), 1.44 (3H, s, isopropylidene-CH_3), 4.37 (1H, d, 5-Ha, J_{gem} = 17.8 Hz), 4.55 (1H, d, 5-Hb, J_{gem} = 17.8 Hz), 5.03 (1H, d, 3-H, $J_{2,3}$ = 6.6 Hz), 5.71 (1H, d, 2-H, $J_{2,3}$ = 6.6 Hz), 7.24−8.11 (10H, m, PhH, indole). Anal. Calcd for $C_{28}H_{35}O_7NSSi$: C, 60.30; H, 6.33; N, 2.51. Found: C, 60.45; H, 6.50; N, 2.55.

Reductive Amination of 7 to give Azasugar 8. Typical Procedure. Ammonium formate (3 mmol), $NaBH_3CN$ (3 mmol), powdered molecular sieves (3A) (100 mg), and **7** were dissolved in MeOH (10 mL). After stirring for 18 h at room temperature, the reaction mixture was filtrated through Celite (Wako hyflo super-cell), extracted with chloroform, and dried over Na_2SO_4. The solvent was removed, and the residue was purified by pTLC (AcOEt/hexane, 1/3) to give **8**.

5-*O*-(*tert*-Butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-(2-thienyl)-D-ribitol (8a): oil; IR (neat) 840, 1080, 1250, 1370, 1780, 2900 cm^{-1}; HRMS (FAB, NBA) calcd for $C_{18}H_{32}O_3NSSi$ *m/e* (M + H) 370.1872, found 370.1880; ^{1}H NMR (500 MHz, $CDCl_3$) (β-form) δ 0.08 (6H, s, TBDMS Si-Me), 0.91 (9H, s, TBDMS Si-^{t}Bu), 1.30 (3H, s, isopropylidene-CH_3), 1.53 (3H, s, isopropylidene-CH_3), 1.91 (1H, bs, N-H), 3.04 (1H, ddd, 4-H, $J_{3,4}$ = 4.4 Hz, $J_{4,5a}$ = 6.9 Hz, $J_{4,5b}$ = 5.8 Hz), 3.83 (1H, dd, 5-Ha, $J_{4,5a}$ = 6.9 Hz, J_{gem} = 9.9 Hz), 3.93 (1H, dd, 5-Hb, $J_{4,5b}$ = 5.8 Hz, J_{gem} = 9.9 Hz), 4.21 (1H, d, 1-H, $J_{1,2}$ = 4.1 Hz), 4.65 (1H, dd, 2-H, $J_{1,2}$ = 4.1 Hz, $J_{2,3}$ = 5.5 Hz), 4.69 (1H, dd, 3-H, $J_{2,3}$ = 5.5 Hz, $J_{3,4}$ = 4.4 Hz), 6.97 (1H, m, thiophene 4′-H), 7.05 (1H, m, thiophene 3′-H), 7.26 (1H, m, thiophene 5′-H). Anal. Calcd for $C_{18}H_{32}O_3NSSi$: C, 58.33; H, 8.71; N, 3.78. Found: C, 58.16; H, 8.89; N, 3.55.

1-(2-Benzofuryl)-5-*O*-(*tert*-butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-ribitol (8b): oil; IR (neat) 830, 1070, 1240, 1420, 1780, 2890 cm^{-1}; HRMS (FAB, NBA) calcd for $C_{22}H_{34}O_4NSi$ *m/e* (M+H) 404.2257, found 404.2260; ^{1}H NMR (270 MHz, $CDCl_3$): (β-form) δ 0.11 (6H, s, TBDMS Si-Me), 0.92 (9H, s, TBDMS Si-^{t}Bu), 1.30 (3H, s, isopropylidene-CH_3), 1.44 (3H, s, isopropylidene-CH_3), 1.90 (1H, bs, NH), 3.08 (1H, ddd, 4-H, $J_{3,4}$ = 4.3 Hz, $J_{4,5a}$ = 6.6 Hz, $J_{4,5b}$ = 6.3 Hz), 3.89 (1H, dd, 5-Ha, $J_{4,5a}$ = 6.6 Hz, J_{gem} = 9.9 Hz), 3.96 (1H, dd, 5-Hb, $J_{4,5b}$ = 6.3 Hz, J_{gem} = 9.9 Hz), 4.09 (1H, d, 1-H, $J_{1,2}$ = 4.0 Hz), 4.73 (1H, dd, 2-H, $J_{1,2}$ = 4.0 Hz, $J_{2,3}$ = 5.6 Hz), 4.87 (1H, dd, 3-H, $J_{2,3}$ = 5.6 Hz, $J_{3,4}$ = 4.3 Hz), 6.72 (1H, s, benzofuran 3′-H), 7.17−7.54 (4H, m, benzofuran 4′-H, 5′-H, 6′-H, 7′-H). Anal. Calcd for $C_{22}H_{34}O_4NSi$: C, 65.31; H, 8.47; N, 3.46. Found: C, 65.52; H, 8.43; N, 3.53.

5-*O*-(*tert*-Butyldimethylsilyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-1-[2-[*N*-(phenylsulfonyl)indolyl]]-D-ribitol (8c): foam; IR (KBr) 840, 1200, 1380, 1440, 1620, 1720, 2900 cm^{-1}; HRMS (FAB, NBA) calcd for $C_{28}H_{37}O_5N_2SSi$ *m/e* (M − H) 541.2192, found 541.2192; ^{1}H NMR (400 MHz, $CDCl_3$) (β-form) δ 0.11 (6H, s, TBDMS Si-Me), 0.93 (9H, s, TBDMS Si-^{t}Bu), 1.25 (3H, s, isopropylidene-CH_3), 1.37 (3H, s, isopropylidene-CH_3), 1.72 (1H, bs, NH), 3.11 (1H, ddd, 4-H, $J_{3,4}$ = 4.4 Hz, $J_{4,5a}$ = 6.9 Hz, $J_{4,5b}$ = 5.5 Hz), 3.86 (1H, dd, 5-Ha, $J_{4,5a}$ = 6.9 Hz, J_{gem} = 9.9 Hz), 3.97 (1H, dd, 5-Hb, $J_{4,5b}$ = 5.5 Hz, J_{gem} = 9.9 Hz), 4.63 (1H, d, 1-H, $J_{1,2}$ = 4.4 Hz), 4.71 (1H, dd, 2-H, $J_{1,2}$ = 4.4 Hz, $J_{2,3}$ = 5.9 Hz), 5.08 (1H, dd, 3-H, $J_{2,3}$ = 5.9 Hz, $J_{3,4}$ = 4.4 Hz), 6.84−8.03 (10H, m, PhH, indole). Anal. Calcd for $C_{28}H_{37}O_5N_2SSi$: C, 62.07; H, 6.89; N, 5.17. Found: C, 62.23; H, 6.73; N, 5.34.

Deprotection of 8 To Give *C*-Azanucleoside 9. Typical Procedure. Compound **8** (0.5 mmol) was dissolved in aqueous CF_3CO_2H (5 mL, 70% v/v) and stirred at 50 °C for 2 h. The mixture was concentrated, and the residue was purified by pTLC ($CHCl_3$/MeOH, 9/1) to give **9**.

1,4-Dideoxy-1,4-imino-1-(2-thienyl)-D-ribitol (9a): oil; IR (neat) 800, 1020, 1200, 1420, 1660, 3300 cm^{-1}; HRMS (FAB, NBA + NaCl) calcd for $C_9H_{13}O_3NSNa$ *m/e* (M + Na) 238.0514, found 238.0521; ^{1}H NMR (270 MHz, CD_3OD) (β-form) δ 3.75 (1H, m, 4-H), 3.88−3.91 (2H, m, 5-Ha, 5-Hb), 4.31 (1H, dd, 2-H, $J_{1,2}$ = 3.6 Hz, $J_{2,3}$ = 4.3 Hz), 4.58 (1H, dd, 3-H, $J_{2,3}$ = 4.3 Hz, $J_{3,4}$ = 7.7 Hz), 4.81 (1H, d, 1-H, $J_{1,2}$ = 3.6 Hz), 7.06 (1H, m, thiophene 4′-H), 7.33 (1H, m, thiophene 3′-H), 7.49 (1H, m, thiophene 5′-H). Anal. Calcd for $C_9H_{13}O_3NS$: C, 50.21; H, 6.09; N, 6.51. Found: C, 50.40; H, 6.13; N, 6.35.

1-(2-Benzofuryl)-1,4-dideoxy-1,4-imino-D-ribitol (9b): solid; IR (KBr) 800, 1140, 1200, 1670, 3400 cm^{-1}; HRMS (FAB, NBA + NaCl) calcd for $C_{13}H_{15}O_4NNa$ *m/e* (M + Na) 272.0899, found 272.0894; ^{1}H NMR (270 MHz, CD_3OD) (β-form) δ 3.41 (1H, m, 4-H), 3.76−3.85 (2H, m, 5-Ha, 5-Hb), 4.35−4.36 (2H, m, 2-H, 3-H), 4.53 (1H, m, 1-H), 6.86 (1H, s, benzofuran 3′-H), 7.16−7.27 (2H, m, benzofuran 5′-H, 6′-H), 7.43−7.56 (2H, m, benzofuran 4′-H, 7′-H). Anal. Calcd for $C_{13}H_{15}O_4N$: C, 62.64; H, 6.07; N, 5.62. Found: C, 62.53; H, 6.11; N, 5.58.

1,4-Dideoxy-1,4-imino-1-[2-[*N*-phenylsulfonyl)indolyl]]-D-ribitol (9c): solid; IR (KBr) 810, 1030, 1210, 1680, 3300 cm^{-1}; HRMS (FAB, NBA) calcd for $C_{19}H_{21}O_5N_2S$ *m/e* (M + H) 389.1171, found 389.1172; ^1H NMR (400 MHz, CD_3OD) (β-form) δ 3.92 (1H, m, 4-H), 3.99 (2H, m, 5-Ha, 5-Hb), 4.66 (1H, m, 2-H), 4.71 (1H, m, 3-H), 5.42 (1H, d, 1-H, $J_{1,2}$ = 3.6 Hz), 7.25−8.06 (10H, m, PhH, indole). Anal. Calcd for $C_{19}H_{21}O_5N_2S$: C, 58.59; H, 5.44; N, 7.19. Found: C, 58.69; H, 5.28; N, 7.13.

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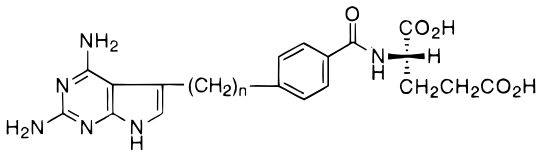
Additions and Corrections

Vol. 60, 1995

Edward C. Taylor,* Hemantkumar H. Patel, and

Jong-Gab Jun. A One-Step Ring Transformation/Ring Annulation Approach to Pyrrolo[2,3-*d*]pyrimidines. A New Synthesis of the Potent DHFR Inhibitor TNP-351.

Pages 6684−6687. Compound **2** was incorrectly identified as TNP-351. The latter has a three-carbon (propyl) bridge between the pyrrole and benzene rings; compound **2** is its lower (ethyl-bridged) homolog, which was first described by Shih and Gossett (Shih, C.; Gossett, L. S. *Heterocycles* **1993**, *35*, 825). A paper describing a synthesis of TNP-351 utilizing our one-step ring transformation/ring annulation reaction will be submitted shortly to this Journal.



2, n = 2
TNP-351, n = 3

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Vol. 61, 1995

Michael J. Rodriguez,* Mark J. Zweifel, and

Richard J. Loncharich*. Aldol-Promoted Reaction of R106-Sarcosine: Synthesis and Conformational Analysis of Novel R106 Analogs.

Page 1566, Table 1. The corrected entries for "acetone" in Table 1 are shown below.

Page 1566, Figure 2. The D/L ratios after 3 and 24 h are 2:1 and 5:1, respectively.

Table 1. Alkylation of R106-Sarcosine, 2 with Ketones

electrophile	product	temp (°C)	Rxn time (h)	salt (8 equiv)	BASE (5 equiv/ 5 equiv)	D/L ratios[a]
acetone	**3**	−78	3	LiCl	LDA/nBuLi	2:1
		−78	24	LiCl	LDA/nBuLi	5:1
		−78 → −45	3	LiCl	LDA/nBuLi	3.3:1
		−78	3	$MgCl_2$	LDA/nBuLi	1:1
		−78	0.5	LiCl	MeLi/−	3:1

[a] D/L ratios of inseparable mixtures of diastereomers were determined by ^1H NMR.

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