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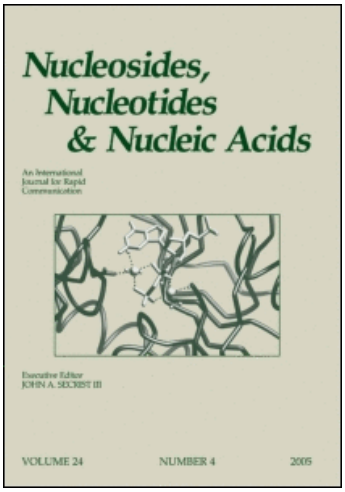

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An Improved Total Synthesis of Triciribine: A Tricyclic Nucleoside with Antineoplastic and Antiviral Properties[†]

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ABSTRACT

We describe an efficient total synthesis of triciribine, a tricyclic nucleoside with antineoplastic and antiviral properties, starting from 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine.

Key Words: Cancer; HIV; Triciribine; TCN; 4-amino-6-bromo-5-cyanopyrrolo[2, 3-d]pyrimidine.

INTRODUCTION

Triciribine (TCN) is a tricyclic nucleoside that was first synthesized by Schram and Townsend in 1971.[1] Initial testing of triciribine and its water soluble prodrug, triciribine 5′-monophosphate[2] (TCN-P), against L1210 cells, a murine leukemia cell

[†]In honor and celebration of the 70th birthday of Professor Leroy B. Townsend.

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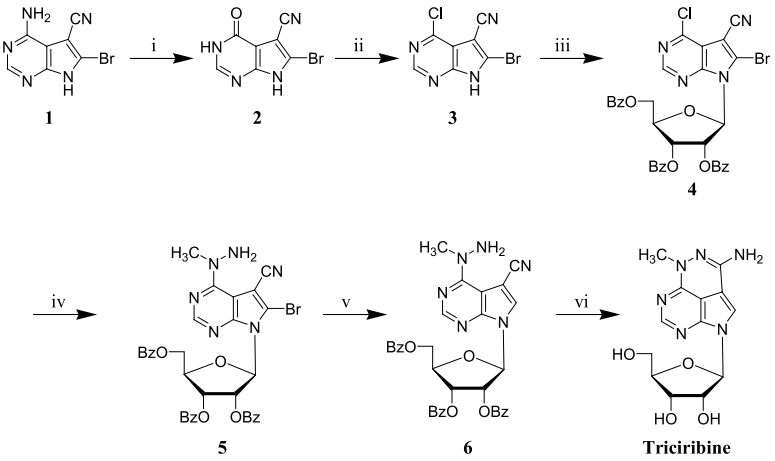
line, revealed their potential as antineoplastic agents. This discovery led to extensive in vitro[3–17] and in vivo[18–22] studies of TCN and TCN-P as novel antineoplastic agents. Phase I clinical trials were completed with TCN-P[23–29] and it was advanced to phase II studies as an antineoplastic agent.[27,29–32] Subsequently, we have found that TCN and TCN-P are selective and potent inhibitors of HIV-1 and HIV-2 in acutely and persistently infected cells.[33] These studies also found no cross resistance to TCN or TCN-P in AZT or TIBO resistant HIV strains[33] suggesting that TCN and TCN-P have an entirely different mode of action than AZT and TIBO. Triciribine was shown to have no activity against the HIV encoded enzymes, reverse transcriptase, RNase H, integrase, and protease.[34] Furthermore, cytotoxicity such as that observed in murine L1210 cells appears to be highly cell line specific and was not observed in human cell lines used to propagate HIV and human cytomegalovirus (HCMV).[33] Even though TCN was not very cytotoxic in these cell lines, it had to be phosphorylated to TCN-P to be active against HIV-1.[34] The antiviral mechanism of action of TCN has yet to be elucidated, but studies are currently underway.[35–38]

Triciribine was originally synthesized from the naturally occurring antibiotic toyocamycin, which has since been unavailable through commercial sources. Though we have recently published[39] a new synthetic procedure for toyocamycin, we felt it would be tedious and inefficient to continue to synthesize triciribine from toyocamycin. Therefore, we report a new and more efficient synthesis of triciribine that bypasses the need for toyocamycin.

DISCUSSION

For the synthesis of triciribine, it was apparent that the original synthetic route, using commercially unavailable toyocamycin as our starting material, would be inefficient. This prompted us to initiate studies designed to develop the new synthetic



Scheme 1. Synthesis of triciribine. Reagents: i) $NaNO_2$, AcOH, H_2O; ii) $POCl_3$; iii) BSA, CH_3CN then 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose, TMSOTf; iv) NH_2NHCH_3, EtOH, $CHCl_3$; v) HCO_2NH_4, 10% Pd-C, EtOH, reflux; vi) NaOMe, MeOH, reflux.

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route illustrated in Scheme 1. 6-Bromo-5-cyanopyrrolo[2,3-*d*]pyrimidin-4-one (**2**) was obtained in 95% yield by diazotizing 4-amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine[39] (**1**) with sodium nitrite in aqueous acetic acid at 105°C for 4 h. Chlorination of compound **2** with phosphorus oxychloride at reflux temperature for 3 h gave a 75% yield of 6-bromo-4-chloro-5-cyanopyrrolo[2,3-*d*]pyrimidine (**3**). By coupling compound **3** to 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose we could avoid the deprotection, protection, and deprotection sequence previously reported.[40,41]

Glycosylation of compound **3** was accomplished, in a similar procedure as previously described[39] for the synthesis of toyocamycin, by first silylating compound **3** with 1.2 equivalents of *N*,*O*-bis(trimethylsilyl)acetamide (BSA) in dry acetonitrile under argon at room temperature. After 10 min, 1 equivalent of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose was added, along with 1.5 equivalents of trimethylsilyl trifluoromethanesulfonate (TMSOTf) under argon at room temperature. After stirring at room temperature for 10 min, the reaction mixture was stirred at 60°C for 2 h to afford 6-bromo-4-chloro-5-cyano-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**4**) in 73% yield. Treatment of compound **4** with methylhydrazine in ethanol at room temperature for 30 min afforded 6-bromo-5-cyano-4-(1-methylhydrazino)-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**5**) in 72% yield. Debromination was accomplished by heating a mixture of compound **5**, ammonium formate, and 10% palladium on charcoal in ethanol at reflux temperature for 1 h to give 5-cyano-4-(1-methylhydrazino)-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-d]pyrimidine (**6**) in 97% yield. Deprotection was accomplished by stirring compound **6** with sodium methoxide in methanol at room temperature for 1 hr and ring closure was achieved by heating the reaction mixture at reflux temperature for 18 hr. Neutralization of the product with Amberlite IR-120 afforded triciribine in 80% yield (29% yield from compound **1**).

EXPERIMENTAL

General procedures. Reaction mixtures were evaporated at 60°C under reduced pressure (water aspirator) using a Buchi R-151 rotary evaporator. Melting points (uncorrected) were obtained on a Laboratory Devices Mel-Temp melting point apparatus. Thin layer chromatography used Analtech GHLF SiO_2 prescored plates. Developed TLC plates were visualized under ultraviolet light (254 nm). Proton magnetic resonance (^{1}H NMR) spectra were obtained with a Brucker Avance DPX 300 or DRX 500 spectrometer (solutions in $CDCl_3$ or DMSO-d_6) with the chemical shifts reported in parts per million downfield from tetramethylsilane as the internal standard. UV spectra were obtained with a Kontron UVIKON 860 ultraviolet spectrometer. Elemental analysis were performed by the Analytical Laboratory, Department of Chemistry, University of Michigan, Ann Arbor, MI.

6-Bromo-5-cyanopyrrolo[2,3-*d*]pyrimidin-4-one (2). 4-Amino-6-bromo-5-cyanopyrrolo[2,3-*d*]pyrimidine[39] (**1**) (2.38 g, 10 mmol) was suspended in a mixture of water (50 mL) and glacial acetic acid (50 mL) and heated to 105°C. Aqueous sodium nitrite (6.9 g in 100 mL water) was added dropwise to the suspension over a period of 2 h and then the mixture was allowed to stir at 105°C for another 2 h. The reaction mixture was cooled to room temperature and then stored at 5°C for 4 h. The precipitate was

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collected by vacuum filtration, resuspended in water, and heated at reflux temperature for 3 h. The reaction mixture was again cooled to room temperature and then stored at 5°C for 4 h. The precipitate was collected by vacuum filtration and dried at 110°C for 12 h in a vacuum oven. Yield = 2.26 g (95%); mp 387°C dec. (lit.[42] mp > 300°C); ^{1}H-NMR (DMSO-d_6) δ 13.83 (bs, 1H, NH), 12.42 (bs, 1H, NH), 8.00 (s, H-2); Anal. Calcd. For $C_7H_3N_4OBr$: C, 35.15; H, 1.26; N, 23.43. Found: C, 35.60; H, 1.41; N, 23.32.

6-Bromo-4-chloro-5-cyanopyrrolo[2,3-*d*]pyrimidine (3). 6-Bromo-5-cyanopyrrolo[2,3-*d*]pyrimidin-4-one (**2**) (1.43 g, 6 mmol) was suspended in phosphorus oxychloride (25 mL) and heated at reflux temperature for 3 h. The reaction mixture was cooled to room temperature and then poured over ice water (150 mL). The mixture was vigorously stirred and maintained at 0°C until all of the phosphorus oxychloride was destroyed. The suspension was stored at 5°C for 1 h and then the precipitate was collected by filtration. The solid was dissolved in hot methanol (100 mL) and recrystallized from a hot mixture of methanol and water. The crystals were collected by filtration and dried for 24 h at 100°C in a vacuum oven. Yield = 1.16 g (75%); mp 268–270°C dec. (lit.[42] mp 250°C); ^{1}H-NMR (DMSO-d_6) δ 13.83 (bs, 1H, NH), 12.42 (bs, 1H, NH), 8.00 (s, H-2).

6-Bromo-4-chloro-5-cyano-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (4). *N*,*O*-Bis(trimethylsilyl)acetamide (BSA, 2.44 g, 1.7 mL, 12 mmol) was added to a stirred suspension of 6-bromo-4-chloro-5-cyanopyrrolo[2,3-*d*]pyrimidine (**3**) (2.58 g, 10 mmol) in dry acetonitrile (100 mL) at room temperature under argon. After 15 min, 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranose (5.0 g, 10 mmol) was added along with trimethylsilyl trifluoromethanesulfonate (TMSOTf, 3.33 g, 2.7 mL, 15 mmol). The suspension was stirred at room temperature for 10 min, heated at 60°C for 2 h and then cooled to room temperature. The solution was diluted with ethyl acetate (100 mL) and poured over saturated sodium bicarbonate (100 mL) at room temperature. The aqueous layer was separated and discarded and the organic layer was washed with brine (100 mL) and dried over magnesium sulfate. After filtration, the solvent was removed and the residue was dissolved in chloroform and eluted from a silica gel column (7 cm (d) × 9 cm (h)) using chloroform as the eluting solvent. Fractions of 100 mL were collected and the UV containing fractions (TLC, 1:3 ethyl acetate:hexane) whose R_f value was 0.41 were combined and evaporated to dryness. The residue was dissolved in dichloromethane (100 mL) and evaporated. The residue was dried in a vacuum oven at 65°C for 12 h to obtain 5.1 g (73% yield) of pure **4**. mp 100°C shrank, 120–145°C melted and resolidified, 184–186°C melted; R_f = 0.41 (1:3 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$) δ 4.70 (1H, dd), 4.90 (1H, m), 4.94 (1H, dd), 6.42 (2H, m), 6.58 (1H, m), 7.30–7.65 (9H, m), 7.85–8.10 (6H, m), 8.57 (1H, s). Anal. Calcd for: $C_{33}H_{22}N_4O_7ClBr$: C, 56.45; H, 3.14; N, 7.98 Found: C, 56.46; H, 3.40; N, 7.93.

6-Bromo-5-cyano-4-(1-methylhydrazino)-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (5). 6-Bromo-4-chloro-5-cyano-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**4**) (4.7 g, 6.7 mmoles) was dissolved in a mixture of chloroform (75 mL) and ethanol (75 mL) and then treated with methylhydrazine (0.74 g, 16 mmol, 0.52 mL). The reaction mixture was allowed to stir

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for 30 min, at which time a white precipitate had formed. The solvent was removed under vacuum and the residue was resuspended in ethanol (200 mL), collected by filtration, washed with ethanol (100 mL). The resulting precipitate was recrystallized from ethanol, collected by filtration, and dried in a vacuum oven at 60°C for 12 h to yield 3.43 g (72%) of pure **5**. mp 173–175°C dec; R_f = 0.44 (1:1 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$) δ 3.51 (3H, s), 4.19 (2H, bs), 4.70 (1H, dd), 4.79 (1H, m), 4.90 (1H, m), 6.43 (1H, s), 6.50 (1H, m), 6.63 (1H, m), 7.40 (6H, m), 7.57 (3H, m), 7.93 (2H, m), 8.02 (4H, m), 8.28 (1H, s). Anal. Calcd for: $C_{34}H_{27}N_6O_7Br \cdot 0.50\ H_2O$: C, 56.67; H, 3.89; N, 11.67; Found: C, 56.55; H, 3.86; N, 11.66.

5-Cyano-4-(1-methylhydrazino)-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (6). 6-Bromo-5-cyano-4-(1-methylhydrazino)-7-[2,3,5-tri-*O*-benzoyl-β-Dribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**5**) (2.82 g, 4.0 mmol), ammonium formate (2.5 g, 40 mmol) and 10% palladium on activated charcoal (280 mg) were suspended in ethanol (100 mL) and the suspension was heated at reflux temperature for 1 h. The hot reaction mixture was filtered through Celite and washed with hot ethanol (100 mL). The solvent was removed and the residue was dissolved in ethyl acetate (100 mL) and extracted with water (100 mL). The water layer was removed and discarded and the ethyl acetate layer was dried over magnesium sulfate. The magnesium sulfate was removed by filtration and the filtrate was evaporated to dryness. The residue was recrystallized from a hot mixture of ethanol and water to yield 2.43 g (97%) of pure **6**. mp 100°C shrank, 120–135°C melted and resolidified, 168–170°C melted; R_f = 0.40 (1:1 ethyl acetate:hexane); ^{1}H NMR ($CDCl_3$) δ 3.51 (3H, s), 4.19 (2H, bs), 4.80 (3H, m), 6.15 (2H, s), 6.64 (1H, d), 7.35–8.35 (17H, m). Anal. Calcd for: $C_{34}H_{28}N_6O_7$: C, 64.56; H, 4.43; N, 13.29. Found: C, 64.35; H, 4.70; N, 13.30.

6-Amino-4-methyl-8-(β-D-ribofuranosyl)pyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine(Triciribine, TCN). 5-Cyano-4-(1-methylhydrazino)-7-[2,3,5-tri-*O*-benzoyl-β-D-ribofuranosyl)pyrrolo[2,3-*d*]pyrimidine (**6**) (1.09 g, 1.72 mmol) and sodium methoxide (0.42 g, 7.75 mmol) were suspended in dry methanol (100 mL) and stirred for 1 h at room temperature under argon. TLC showed the disappearance of starting material and the appearance of a new spot at R_f = 0.28 (9:1 chloroform:methanol). The reaction mixture was heated at reflux temperature, under argon, for 18 h. TLC showed the disappearance of starting material and the appearance of a new spot at R_f = 0.15 (9:1 chloroform:methanol). The solvent was removed under vacuum at 60°C and the yellow residue was suspended in ethyl acetate and stirred at room temperature for 15 min. The precipitate was collected by vacuum filtration, dissolved in hot water (20 mL), and neutralized with Amberlite IR-120. The hot reaction mixture was filtered, cooled to room temperature and then cooled to 5°C for 12 h to crystallize TCN. The crystals were collected by filtration and dried in a vacuum oven at 80°C for 18 h to yield 0.44 g (80%) of pure TCN; mp 207°C dec. (lit.[1] mp 205°C dec); R_f = 0.15 (9:1 chloroform:methanol); UV [λ_{max} (ε)] (pH 1) 286 (10844), 279 (10951), (pH 7) 292 (11822), (pH 11) 290 (12320); ^{1}H NMR (DMSO-d_6) δ 8.02 (1H, s, H-2), 7.06 (1H, s, H-7), 6.27 (2H, s, NH_2), 5.81 (1H, d, H-1′), 5.62 (1H, t, OH), 5.42 (1H, d, OH), 5.22 (1H, m, OH), 4.48 (1H, m), 4.08 (1H, m), 3.96 (1H, m), 3.53 (2H, m), 3.38 (3H, s, NCH_3); Anal. Calcd for: $C_{13}H_{16}N_6O_4 \cdot 0.50\ H_2O$: C, 47.42; H, 5.17; N, 25.53. Found: C, 47.66; H, 5.40; N, 25.16.

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