Communication
An Expedient Total Synthesis of Triciribine

Chen Hu, Zhizhong Ruan, Haixin Ding, Yirong Zhou and Qiang Xiao *

Jiangxi Key Laboratory of Organic Chemistry, Jiangxi Science & Technology Normal University, Nanchang 330013, China; nchuyen@yahoo.com (C.H.); ruanzhizhong87@163.com (Z.R.); dinghaixin_2010@163.com (H.D.); zyrhurst@126.com (Y.Z.)
* Correspondence: xiaoqiang@tsinghua.org.cn; Tel.: +86-791-8642-2903

Academic Editor: Roman Dembinski
Received: 6 March 2017; Accepted: 11 April 2017; Published: 17 April 2017

Abstract: In the present paper, we report an expedient total synthesis of triciribine, a tricyclic 7-deazapurine nucleoside and protein kinase B (AKT) inhibitor, in 35% overall yield. Our synthesis route features a highly regioselective substitution of 1-N-Boc-2-methylhydrazine and a trifluoroacetic acid catalyzed one-pot transformation which combined the deprotection of the tert-butylcarbonyl (Boc) group and ring closure reaction together to give a tricyclic nucleobase motif.

Keywords: triciribine; ring closure; nucleosides; glycosylation; total synthesis

1. Introduction

In the past few decades, a large number of novel nucleosides have been successfully developed as antiviral and antitumor drugs [1,2]. Triciribine (TCN, 1, Figure 1), a unique tricyclic 7-deazapurine nucleoside, was firstly synthesized by Townsend in 1971 [3]. Initial biological evaluation of TCN showed excellent activity against murine leukemia cell line L1210 [4]. In order to improve the bioavailability, TCN-P (triciribine phosphate monohydrate, 2, Figure 1) was further developed to enhance its solubility in water. In the late 1980s, TCN-P was thoroughly studied as a cytotoxic agent in a phase I clinical trial for cancer treatment [5,6]. Unfortunately, it was precluded during the phase II clinical trial in the early 1990s because of its poor toxicity profile and mild efficacy [7,8].

![Figure 1. Structures of triciribine 1 and triciribine monophosphate 2.](image)

In recent years, TCN-P was reinvestigated as an efficient inhibitor of the protein kinase B (AKT) signaling pathway [9]. It was found that AKT would be over activated in a high percentage of leukemia tumors and a wide range of other solid tumors, including breast, ovarian and pancreatic cancers, etc. [10]. Currently, it is undergoing a phase I/IIa clinical trial for the treatment of breast cancer and pancreatic cancer [11].

During our development of a new triciribine prodrug for discovering a potential enhanced AKT inhibitor, ten grams’ scale of triciribine was necessary as a starting material. Therefore, an expedient synthetic procedure was in high demand. However, to the best of our knowledge, there were only three publications concerning its preparation. In the original paper by Townsend [2], the naturally...
occurring nucleoside toyocamycin was used as starting material, which is extremely expensive. Thirty years later, they reported an improved synthetic approach in 2004 [12]. 6-Bromo-4-chloro-5-cyano-pyrrolo[2,3-d]pyrimidine 4 was employed as the nucleoside base to afford nucleoside 5 in high yield and stereoselectivity under standard Vorbrüggen glycosylation condition. Further reaction with methylhydrazine gave nucleoside 6 with exclusive regioselectivity (Scheme 1). After debromination with 10% palladium on charcoal, triciribine was accomplished in moderate yield by refluxing with sodium methoxide in methanol. Later, TSRL Inc. reported another expedient total synthesis approach in 2011 [13]. The key step was the selective introduction of cyanation at 7-position of the deazapurine using tributyltin cyanide and palladium tetraphenylphosphine. Because nucleobase 4-chloro-5-ido-7H-pyrrolo[2,3-d]pyrimidine is commercially available, it could easily scale up triciribine’s preparation. The drawback is that transition-metal-catalyzed cyanation will cause heavy metal residue, which is cumbersome to remove completely [14]. In the present paper, a new expedient total synthesis of triciribine was developed.

Scheme 1. Synthesis of triciribine intermediate. Reagents and conditions: (a) Method A: N,O-Bis(trimethylsilyl)acetamide (BSA), CH3CN, trimethylsilyl trifluoromethanesulfonate (TMSOTf), 80 °C, 70%; Method B: BSA, CH3CN, TMSOTf, microwave heating, 80 °C, 68%; Method C: BSA, CH3CN, nonafluorobutane sulfonic acid potassium, TMSCl, microwave heating, 80 °C, 63%; (b) NH2NHCH3, CHCl3, EtOH, r.t., 60% (6), 16% (7).

2. Results and Discussion

In our foregoing synthesis of 7-deazapurine nucleoside [15–17], our group gained rich experiences in the process of preparing 6-bromo-4-chloro-5-cyano-pyrrolo[2,3-d]pyrimidine 4 in 100 g scale. At the beginning, we tried to synthesize triciribine by Townsend’s approach (Scheme 1). Thus, nucleobase 4 was firstly silylated with N,O-bis(trimethylsilyl) acetamide (BSA) in anhydrous CH3CN. Then 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 3 was added to the above homogeneous solution, followed by the slow addition of trimethylsilyl trifluoromethanesulfonate (TMSOTf). Subsequently, the reaction mixture was heated to 80 °C for 10 h, and 7-deazapurine nucleoside 5 was obtained successfully with 70% yield. During our extensive optimization of glycosylation, it was found that the combination of nonafluorobutane sulfonic acid potassium and trimethylsilyl chloride was superior to TMSOTf and that microwave heating can speed up the reaction. With sufficient nucleoside 5 in hand, it was then reacted with methylhydrazine in ethanol. To our surprise, besides the desired nucleoside 6 with 60% yield, another byproduct 7 was also separated in 16% yield. The structure of nucleoside 7 was established by high resolution mass spectroscopy (HRMS ) and various NMR spectra. Because of the electron withdrawing properties of the cyano group, the neighbouring 8-bromo group could be easily substituted by the nucleophilic reagent. This phenomenon was also found in other 7-deazapurine nucleosides [18–20]. To depress the side reaction, various methylhydrazine from different commercial
sources and a variety of solvents were investigated. However, the results showed that it seemed impossible to exclude the side reaction completely.

To improve the total synthetic yield of triciribine, we reasoned that a practicable way could be by decreasing the nucleophilicity of methylhydrazine to alleviate the side reaction (Scheme 2). Commercially available 1-N-Boc-2-methylhydrazine has an electron-withdrawing tert-butylcarbonyl (Boc) group at N-1 position, which could reduce the NH-2 nucleophilicity of methylhydrazine [21–24]. To our delight, nucleoside 9 could be obtained in 89% after treating nucleoside 5 with 1-Boc-2-methylhydrazine by using triethylamine as a base in a mixture solvent of anhydrous dichloromethane (DCM) and ethanol. The 8-bromo substituted side product was not detected. Then, trifluoroacetic acid (TFA) was utilized to remove the Boc group. It was surprising to find that the tricyclic nucleoside 10 was generated directly by the TFA promoted ring closure reaction in situ. In the previously reported literature [12,13], the tricyclic nucleobase motif was achieved by heating nucleoside 6 with sodium methoxide in methanol at reflux temperature for 18 h. Then, debromination was accomplished with 10% Pd/C in ethanol under refluxing for 5 h to afford nucleoside 11 with 83% yield. At last, treatment 11 with sodium methoxide in methanol at room temperature provided triciribine 1 in 92% yield. For the first time, a suitable single crystal of triciribine 1 was obtained from methanol and H2O (10:1) and its structure is unambiguously confirmed by X-ray diffraction analysis (Figure 2) [25]. It exhibits a syn glycosyl bond conformation, which is stabilized by an intramolecular O–H···N hydrogen bond.

\[
\text{Scheme 2. Total synthesis of triciribine 1. Reagents and conditions: (a) CH}_3\text{NHNHBoc, CH}_2\text{Cl}_2, \text{EtOH, triethylamine (TEA), reflux, 89%; (b) trifluoroacetic acid (TFA), CH}_2\text{Cl}_2, \text{r.t., 74%; (c) 10% Palladium on carbon (Pd/C), TEA, THF, CH}_3\text{OH, H}_2, \text{r.t., 83%; (d) CH}_3\text{ONa, CH}_2\text{Cl}_2, \text{CH}_3\text{OH, r.t., 92%}.}
\]

Figure 2. X-ray crystal structure of triciribine.
3. Materials and Methods

All the chemicals and compounds were used as received except for special notification. $^1$H NMR spectra and $^{13}$C NMR spectra were recorded on a Bruker Advanced DPX spectrometer (400 MHz for $^1$H NMR and 100 MHz for $^{13}$C NMR, Bruker Corporation, Billerica, MA, USA). Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constants (Hz) and integration. $^{13}$C NMR spectra were recorded with complete proton decoupling. HRMS was measured on AB Sciex 4600 mass spectrometer equipped with an ESI source in the positive-ion mode (Bruker Corporation, Billerica, MA, USA). Melting points were measured on an X-4 digital melting point apparatus (Beijing Taike Corporation, Beijing, China). The microwave synthesizer was equipped with Anton Paar autosampler MAS24 Monowave 300 (Anton Paar GmbH, Graz, Austria). X-ray analysis was recorded on Bruker Smart Apex II (Bruker Corporation, Billerica, MA, USA). Specific rotation was recorded on Rudolph Autopol IV (Rudolph Research Analytical, Hackettstown, NJ, USA).

3.1. Synthesis of 6-Bromo-4-chloro-5-cyano-7-[2,3,5-tri-O-benzoyl-β-D-ribofuranosyl]pyrrolo[2,3-d]pyrimidine (5)

**Method A:** 6-Bromo-4-chloro-5-cyano-pyrrolo[2,3-d]pyrimidine 4 (257 mg, 1 mmol) was suspended in freshly distilled dry acetonitrile (15 mL) and then $N,O$-bis(trimethylsilyl)acetamide (BSA, 2.44 g, 12 mmol) was added to the reaction under an argon atmosphere. The reaction mixture was stirred at room temperature for 10 min. Then 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 3 (770 mg, 1.5 mmol) was added along with trimethylsilyl trifluoromethanesulfonate (TMSOTf, 890 mg, 4 mmol). After stirring for 15 min, the mixture was heated at 80 °C for 4 h until Thin layer chromatography (TLC) analysis showed that the starting material was consumed completely. Then it was cooled to room temperature, quenched with iced water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with saturated sodium bicarbonate aqueous solution (30 mL) and brine (30 mL), respectively, and dried over magnesium sulfate. After filtration, the solvent was removed under vacuum. The crude product was dissolved in chloroform and purified by silica gel column chromatography to provide the product 5 as a white solid 490 mg, 70% yield.

**Method B:** 6-Bromo-4-chloro-5-cyano-pyrrolo[2,3-d]pyrimidine 4 (257 mg, 1 mmol) was suspended in freshly distilled dry acetonitrile (15 mL) and then $N,O$-bis(trimethylsilyl)acetamide (2.44 g, 12 mmol) was added to the reaction under an argon atmosphere. The reaction mixture was stirred at room temperature for 10 min. Then 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 3 (770 mg, 1.5 mmol) was added along with trimethylsilyl trifluoromethanesulfonate (TMSOTf, 890 mg, 4 mmol). Then the reaction mixture was transferred to a microwave synthesizer, and heated at 80 °C for 50 min until TLC analysis showed that the starting material was consumed completely. Then it was cooled to room temperature, quenched with ice water (20 mL) and extracted with ethyl acetate (15 mL × 3). The combined organic layer was washed with saturated sodium bicarbonate aqueous solution (30 mL) and brine (30 mL), respectively, and dried over magnesium sulfate. After filtration, the solvent was removed under vacuum. The crude product was dissolved in chloroform and purified by silica gel column chromatography to provide the product 5 as a white solid 477 mg, 68% yield.

**Method C:** $N,O$-Bis(trimethylsilyl)acetamide (1.38 g, 6.8 mmol), 6-bromo-4-chloro-5-cyano-pyrrolo pyrimidine 4 (460 mg, 1.95 mmol), 1-O-acetyl-2,3,5-tri-O-benzoyl-β-D-ribofuranose 3 (1.55 g, 3.1 mmol), nonafluorobutane sulfonic acid potassium (3.2 g, 9.4 mmol) and trimethylsilyl chloride (TMSCl, 1.02 g, 9.4 mmol) were added in freshly distilled dry acetonitrile (15 mL). Then the reaction mixture was transferred to a microwave synthesizer, and heated at 80 °C for 50 min until TLC analysis showed that the starting material was consumed completely. Then it was cooled to room temperature, quenched with ice water (20 mL) and extracted with ethyl acetate (20 mL × 3). The combined organic layer was washed with saturated sodium bicarbonate aqueous solution (30 mL) and brine (30 mL), respectively, and dried over magnesium sulfate. After filtration, the solvent was removed under vacuum. The crude product was dissolved in chloroform and purified by silica gel column chromatography to provide the product 5 as a white solid 477 mg, 68% yield.
product was dissolved in chloroform and purified by silica gel column chromatography to provide the product 5 as a white solid 800 mg, 63% yield.

Retention factor (Rf) = 0.4 (CH2Cl2/EtOAc, 40:1); m.p. 88–91 °C (Lit.9 100 °C); [α]D25 + 32.184 (c = 0.087 g/100 mL, EtOAc); 1H NMR (400 MHz, DMSO-d6) δ: 8.70 (s, 1H, H-2), 7.95–7.83 (m, 6H), 7.67–7.64 (m, 3H), 7.50–7.40 (m, 6H), 6.59 (d, J = 3.2 Hz, 1H, H-1′), 6.35 (dd, J = 6.0, 3.2 Hz, 1H, H-2′), 6.41 (t, J = 6.8 Hz, 1H, H-3′), 4.93 (dt, J = 7.2, 3.6 Hz, 1H, H-4′), 4.84 (dd, J = 12.4, 2.8 Hz, 1H, H-5′), 4.60 (dd, J = 12.4, 4.2 Hz, 1H, H-5′). 13C NMR (100 MHz, DMSO-d6) δ: 165.7, 165.1, 152.9 (C-6), 150.8 (C-2), 150.7 (C-4), 143.5, 143.4, 143.9, 129.9, 129.8, 129.5, 129.3, 129.2, 129.1, 128.9, 128.8, 116.9 (C-8), 113.2 (CN), 101.8 (C-5), 89.8 (C-1′), 89.5 (C-7), 79.6 (C-4′), 73.6 (C-2′), 70.3 (C-3′), 62.8 (C-5′); MS (ESI) m/z: 702.9 [M + H]+. HR-MS: calcld. for C33H22BrClN4O7 [M + Na]+ 725.0235; found: 725.0239.

3.2. Synthesis of 6-Bromo-5-cyano-4-(1-methylhydrazino)-7-[2,3,5-tri-O-benzoyl-D-ribofuranosyl]pyrrolo[2,3-d]pyrimidine (6)

6-Bromo-4-chloro-5-cyano-7-[2,3,5-O-tribenzoyl-D-ribofuranosyl]pyrrolo[2,3-d]pyrimidine 5 (0.47 g, 0.67 mmol) was dissolved in a mixture of chloroform (7.5 mL) and ethanol (7.5 mL), then the reaction mixture was treated with the solution of methyl hydrazine (40%, 0.24 g, 2.08 mmol). The reaction was stirred at room temperature for 3 h while a white precipitate was formed. TLC analysis showed that the starting material was consumed completely. The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography to provide the product 5 as a white solid. 286 mg, 60% yield; Rf = 0.5 (CH2Cl2/EtOAc, 30:1); m.p. 192–195 °C; [α]D25 + 45.763 (c = 0.118 g/100 mL, CH2Cl2); 1H NMR (400 MHz, DMSO-d6) δ: 8.13 (s, 1H, H-2), 7.91 (t, J = 6.4 Hz, 6H), 7.65 (t, J = 7.2 Hz, 3H), 7.54–7.37 (m, 6H), 6.58 (d, J = 4.0 Hz, 1H, H-1′), 6.43 (d, J = 8.0 Hz, 1H, H-2′), 6.39 (d, J = 8.0 Hz, 1H, H-3′), 5.25 (s, 2H, NH2), 4.91–4.83 (m, 1H, H-4′), 4.78 (d, J = 12.2, 1H, H-5′), 4.60 (dd, J = 12.0, 4.0 Hz, 1H, H-5′), 3.35 (s, 3H, CH3). 13C NMR (100 MHz, DMSO-d6) δ: 165.8, 165.2, 157.2 (C-6), 152.8 (C-2), 151.4 (C-4), 134.5, 134.3, 134.0, 129.9, 129.8, 129.7, 129.3, 129.2, 129.1, 128.9, 121.9, 116.6 (CN), 101.5 (C-5), 94.2 (C-1′), 89.7, 79.1 (C-4′), 73.5 (C-2′), 70.5 (C-3′), 63.0 (C-5′), 40.6 (CH3). MS (ESI) m/z: 711.1 [M + H]+. HR-MS: calcld. for C34H27BrN5O6 [M + Na]+ 733.1017; found: 733.1028.

Besides the desired product 6, a small amount of by-product 7 was isolated. 22 mg 16% yield. Rf = 0.53 (CH2Cl2 / EtOAc, 30:1); m.p. 189–192 °C; [α]D25 + 57.843 (c = 0.102 g/100 mL, CH2Cl2); 1H NMR (400 MHz, DMSO-d6) δ: 8.41 (s, 1H, H-2), 7.90 (dd, J = 14.8, 7.4 Hz, 6H), 7.68–7.62 (m, 3H), 7.51–7.40 (m, 6H), 6.99 (d, J = 3.4 Hz, 1H, H-1′), 6.56-6.54 (m, 1H, H-2′), 6.35-6.32 (m, 1H, H-3′), 5.37 (s, 2H, NH2), 4.84–4.76 (m, 1H, H-4′), 4.74 (dd, J = 6.8, 4.0 Hz, 1H, H-5′), 4.61 (dd, J = 12.0, 4.4 Hz, 1H, H-5′), 3.42 (s, 3H, CH3). 13C NMR (100 MHz, DMSO-d6) δ: 165.8, 165.1, 165.0, 157.3, 150.7 (C-2), 150.5, 147.2, 134.33, 134.29, 134.0, 129.84, 129.77, 129.71, 129.67, 129.21, 129.18, 129.15, 129.1, 117.2, 115.5 (CN), 88.4 (C-1′), 78.8, 73.2 (C-4′), 70.5 (C-2′), 66.5 (C-3′), 63.2 (C-5′), 45.5 (CH3). HR-MS: calcld. for C34H27ClIN5O7 [M + Na]+ 689.1522; found: 689.1532.

3.3. Synthesis of 6-Bromo-5-cyano-4-(2-(tert-butoxycarbonyl)-1-methylhydrazinyl)-7-[2,3,5-tri-O-benzoyl-D-ribofuranosyl]pyrrolo[2,3-d]pyrimidine (9)

6-Bromo-4-chloro-5-cyano-7-[2,3,5-O-tribenzoyl-D-ribofuranosyl]pyrrolo[2,3-d]pyrimidine 5 (1.75 g, 2.5 mmol), 1-Boc-2-methylhydrazine (0.44 g, 3 mmol) and triethylamine (TEA, 0.3 g, 3 mmol) were added in the mixture of CH2Cl2 (25 mL) and anhydrous C2H5OH (25 mL). The reaction mixture was refuxed under an argon atmosphere for 72 h. TLC analysis showed that the starting material was consumed and a new spot appeared. The mixture was poured over saturated sodium bicarbonate solution (40 mL × 2) and extracted with dichloromethane (50 mL × 3), the organic layer was then washed with brine (30 mL × 2) and dried over magnesium sulfate. After filtration, the solvent was removed under vacuum. The crude product was dissolved in dichloromethane and purified by silica gel column chromatography to provide the product 9 as a white solid. 1.82 g, 89% yield; Rf = 0.4 (CH2Cl2/EtOAc, 80:1); m.p. 120–123 °C; [α]D25 + 41.379 (c = 0.087 g/100 mL, CH3OH); 1H NMR (400 MHz, DMSO-d6) δ:
9.68 (s, 1H, NH), 8.29 (s, 1H, H-2), 7.91 (d, J = 6.0 Hz, 6H), 7.67–7.63 (m, 3H), 7.49–7.43 (m, 6H), 6.55 (s, 1H, H-2'), 6.48 (s, 1H, H-1'), 6.42 (s, 1H, H-3'), 4.89–4.87 (m, 1H, H-4'), 4.78 (d, J = 12.2 Hz, 1H, H-5'), 4.61 (d, J = 8.8 Hz, 1H, H-5'), 3.29 (s, 3H, 6-N-CH3), 1.44 (s, 9H, Boc). 13C NMR (100 MHz, DMSO-d6) δ: 165.5, 164.9, 164.8, 156.9, 155.2, 152.4, 151.2 (C-2), 134.1, 134.0, 133.6, 129.52, 129.48, 129.3, 128.91, 128.86, 128.81, 128.7, 128.6, 124.0, 114.9 (CN), 101.1, 90.9, 89.6 (C-1'), 81.0 (Boc), 78.9 (C-4'), 73.2 (C-2'), 70.1 (C-3'), 62.7 (C-5'), 37.9 (CH3), 28.0 (Boc). MS (ESI) m/z: 811.0 [M + H]+. HR-MS: calcd. for C39H32BrN6O6 [M + Na]+ 833.1541; found: 833.1552.

3.4. Synthesis of 6-Amino-7-bromo-4-methyl-8-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (10)

Nucleoside 9 (1.73 g, 2.1 mmol) was added in the mixture of trifluoroacetic acid (TFA, 20 mL) and dichloromethane (20 mL). The reaction mixture was stirred at room temperature for 2 h. TLC showed that the starting material was consumed and a new spot appeared. The mixture was poured over water (100 mL) and extracted with dichloromethane (50 mL × 2). The organic layer was neutralized with triethylamine and dried over magnesium sulfate. After filtration, the solvent was removed under vacuum. The crude product was dissolved in dichloromethane and purified by silica gel column chromatography to provide the product 10 as a white solid. 1.3 g, 74% yield; Rf = 0.4 (CH2Cl2/EtOAc, 40:1); m.p. 102–105 °C; [a]D25 −34.426 (c = 0.122 g/100 mL, CH3OH); 1H NMR (400 MHz, DMSO-d6) δ: 8.03 (s, 1H, H-7), 7.94–7.88 (m, 6H), 7.67–7.63 (m, 3H), 7.48–7.41 (m, 6H), 6.79 (t, J = 3.6 Hz, 1H, H-1'), 6.39 (t, J = 6.2 Hz, 1H, H-2'), 6.33 (d, J = 3.4 Hz, 1H, H-3'), 5.87 (s, 2H, NH2), 4.85 (d, J = 2.8 Hz, 1H, H-4'), 4.77 (d, J = 12.0 Hz, 1H, H-5'), 4.56 (dd, J = 12.2, 3.4 Hz, 1H, H-5), 3.38 (s, 3H, CH3). 13C NMR (100 MHz, DMSO-d6) δ: 165.8, 165.1, 165.0, 157.0, 150.7, 145.7, 147.4, 146.6 (C-3), 134.4, 134.3, 133.8, 129.83, 129.76, 129.6, 129.2, 129.1, 129.0, 128.8, 109.3, 105.1, 93.2 (C-2), 88.1 (C-1'), 79.3 (C-4'), 72.9 (C-2'), 70.6 (C-3'), 62.9 (C-5'), 35.8 (CH3). MS (ESI) m/z: 711.0 [M + H]+. HR-MS: calcd. for C34H27BrN6O7 [M + Na]+ 733.1017; found: 733.1014.

3.5. Synthesis of 6-Amino-4-methyl-8-(2,3,5-tri-O-benzoyl-β-D-ribofuranosyl)pyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (11)

Nucleoside 10 (1.2 g, 1.45 mmol), triethylamine (0.734 g, 7.3 mmol), and 10% palladium on activated charcoal (180 mg) were added in a mixture of tetrahydrofuran (THF) (20 mL) and methanol (10 mL). The reaction mixture was stirred at room temperature under H2 atmosphere (1 atm) for 3 h. TLC analysis showed that the starting material was consumed completely. The reaction mixture was filtered through Celite and washed with hot ethanol (50 mL). The solvent was removed under vacuum and the crude product was purified by silica gel column chromatography to provide the product 11 as a white solid. 0.9 g, 83% yield; Rf = 0.2 (CH2Cl2/ EtOAc, 1:1); m.p. 104–107 °C; [a]D25 +8.492 (c = 0.107 g/100 mL, CH3OH); 1H NMR (400 MHz, DMSO-d6) δ 8.02 (s, 1H, H-7), 8.01–7.86 (m, 6H), 7.70–7.59 (m, 3H), 7.46–7.44 (m, 6H), 7.16 (s, 1H, H-2), 6.55 (d, J = 4.2 Hz, 1H, H-1'), 6.48 (t, J = 5.2 Hz, 1H, H-2'), 6.30 (s, 2H, NH2), 6.21 (t, J = 5.8 Hz, 1H, H-3'), 4.90–4.80 (m, 1H, H-4'), 4.76 (dd, J = 12.2, 2.8 Hz, 1H, H-5'), 4.64 (dd, J = 12.2, 4.2 Hz, 1H, H-5), 3.40 (s, 3H, CH3). 13C NMR (100 MHz, DMSO-d6) δ 165.7, 164.9, 164.8, 156.5, 151.2, 146.6, 145.8, 134.2, 134.1, 133.1, 129.61, 129.58, 129.53, 129.45, 129.0, 128.96, 128.9, 128.8, 128.6, 111.0, 109.2, 104.3, 88.2 (C-1'), 79.2 (C-4'), 73.4 (C-2'), 70.9 (C-3'), 63.5 (C-5'), 35.5 (CH3). MS (ESI) m/z: 633.2 [M + H]+. HR-MS: calcd. for C34H28N6O7 [M + Na]+ 655.1912; found: 655.1924.

3.6. Synthesis of 6-Amino-4-methyl-8-(β-D-ribofuranosyl)pyrrolo[4,3,2-de]pyrimido[4,5-c]pyridazine (Triciribine, TCN, 1)

Nucleoside 11 (1.5 g, 2.0 mmol) and sodium methoxide (0.65 g, 12 mmol) were added in a mixture of CH2Cl2 (5 mL) and CH3OH (20 mL). The reaction mixture was stirred at room temperature for 2 h until TLC analysis showed that the starting material was consumed completely. The solvent was removed under vacuum and the yellow residue was suspended in ethyl acetate (10 mL), and neutralized with
glacial acetic acid. The residue was filtered and washed with deionized water (10 mL × 3), and dried under vacuum at 80 °C to provide the target product TCN, 1 as a white solid. 0.60 g, 92% yield; Rf = 0.3 (CH2Cl2/CH3OH, 10:1); m.p. 149–150 °C; [α]25°D = −70.248 (c = 0.121 g/100 mL, CH3OH); 1H NMR (400 MHz, DMSO-d6): δ: 8.03 (s, 1H, H-7), 7.07 (s, 1H, H-2), 6.28 (s, 2H, NH2), 5.81 (d, J = 8.0 Hz, 1H, H-1′), 5.63 (q, J = 4.0 Hz, 1H, H-2′), 5.41 (d, J = 4.0 Hz, 1H, H-3′), 5.22 (d, J = 4.0 Hz, 1H, H-4′), 4.51–4.47 (dd, J = 12.0, 8.0 Hz, 1H, H-5′), 4.10 (q, J = 4.0 Hz, 1H, H-5′), 3.98–3.96 (m, 1H, OH), 3.67–3.62 (m, 1H, OH), 3.59–3.52 (m, 1H, OH), 3.39 (s, 3H, CH3). 13C NMR (100 MHz, DMSO-d6): δ: 156.3, 151.6, 146.4, 146.3, 110.8, 109.6, 103.8, 90.0 (C-1′), 86.5 (C-4′), 74.4 (C-2′), 71.5 (C-3′), 62.5 (C-5′), 35.7 (CH3).

HR-MS: calcd. for C13H16N6O4 [M + H]+ 321.1306; found: 321.1306.

4. Conclusions
In summary, an expedient total synthesis of triciribine was accomplished with 35% total yield. Its merits include: (1) 1-N-Boc-6-methylhydrazide could selectively substitute 6-chloro group of nucleoside 5 in high yield without any detectable side product; (2) deprotection of the Boc group with TFA could facilitate the ring closure reaction in a one-pot operation to give the tricyclic nucleoside motif; (3) the current newly developed approach has high overall yield and producibility. Developing novel prodrugs of triciribine to discover a potential enhanced AKT inhibitor is undergoing in our group.

Acknowledgments: We thank the National Science Foundation of China (No. 21462019 and No. 21676131), the Bureau of Science & Technology of Jiangxi Province (20143ACB20012), the China Postdoctoral Science Foundation (No. 2015M570566) and the Jiangxi Province Postdoctoral Science Foundation (No. 2015KY02) for financial support.

Author Contributions: Q.X. conceived and designed the experiments; C.H. and Z.R. performed the experiments; H.D. and Y.Z. analyzed the data; Q.X. wrote the paper.

Conflicts of Interest: The authors declare no conflict of interest.

References and Note
1. De Clercq, E. The next ten stories on antiviral drug discovery (part E): Advents, advances, and adventures. Med. Res. Rev. 2010, 31, 118–160. [CrossRef] [PubMed]
2. De Clercq, E. Antiretroviral drugs. Curr. Opin. Pharmacol. 2010, 10, 507–515. [CrossRef] [PubMed]
3. Schram, K.H.; Townsend, L.B. The synthesis of 6-amino-4-methyl-8-(β-D-ribofuranosyl)(4-H,8-H)pyrrolo pyrimido[4,5-c]pyridazine, a new tricyclic nucleoside. Tetrahedron Lett. 1971, 49, 4757–4760. [CrossRef]
4. Wotring, L.L.; Passiatore, J.E.; Roti Roti, J.L.; Townsend, L.B. Effects of the tricyclic nucleoside 6-amino-4-methyl-8-(β-D-ribofuranosyl)pyrrolo[4,3,-de]pyrimido[4,5-c]pyridazine on the viability and cell cycle distribution of L1210 cells in vitro. Cancer Res. 1985, 45, 6355–6361. [PubMed]
5. Mittelman, A.; Casper, E.S.; Young, C.W. Phase I study of triciribine phosphate nucleoside. Cancer Treat. 1983, 67, 159–162.
6. Feun, L.G.; Savaraj, N.; Bodey, G.P.; Krakoff, I. Phase I study of triciribine phosphate nucleoside using a five-day continuous infusion schedule. Cancer Res. 1984, 44, 3608–3612. [PubMed]
7. O’Connell, M.J.; Rubin, J.; Moertel, C.G. Phase II clinical of triciribine for advanced colorectal cancer. Cancer Treat. 1987, 71, 333–334.
8. Feun, L.G.; Blessing, J.A.; Barrett, R.J.; Hanjani, P.A. A Phase II trial of triciribine nucleoside phosphate in patients with advanced squamous cell carcinoma of the cervix: A gynecologic oncology group study. Am. J. Clin. Oncol. 1993, 16, 506–508. [CrossRef] [PubMed]
9. Yang, L.; Dan, H.C.; Sun, M.; Herlyn, M.; Sebti, S.M.; Cheng, J.Q. Akt/Protein kinase B signaling inhibitor-2, a selective small molecule inhibitor of Akt signaling with antitumor activity in cancer cells overexpressing Akt. Cancer Res. 2004, 64, 4394–4399. [CrossRef] [PubMed]
10. Kim, R.; Yamauchi, T.; Husain, K.; Sebti, S.; Malafa, M. Triciribine phosphate monohydrate, an AKT inhibitor, enhances gemcitabine activity in pancreatic cancer cells. Anticancer Res. 2015, 35, 4599–4604. [PubMed]
11. Christopher, R.G.; Domenico, C.; Robert, M.W. Phase I pharmacokinetic and pharmacodynamic study of triciribine phosphate monohydrate, a small-molecule inhibitor of AKT phosphorylation, in adult subjects with solid tumors containing activated AKT. Investig. New Drugs 2011, 29, 1381–1389.
12. Porcari, A.R.; Townsend, L.B. An improved total synthesis of triciribine: A tricyclic nucleoside with anticancer and antiviral properties. *Nucleosides Nucleotides Nucleic Acids* 2004, 23, 31–39. [CrossRef] [PubMed]

13. Shen, W.; Kim, J.S.; Hilfinger, J. Expedient total synthesis of triciribine and its prodrugs. *Synth. Commun.* 2012, 42, 358–374. [CrossRef]

14. Magano, J.; Dunetz, J.R. Large-scale applications of transition metal-catalyzed couplings for the synthesis of pharmaceuticals. *Chem. Rev.* 2011, 111, 2177–2250. [CrossRef] [PubMed]

15. Sun, J.Y.; Dou, Y.H.; Xiao, Q. First total synthesis of a naturally occurring iodinated 5′-deoxyxylofuranosyl marine nucleoside. *Mar. Drugs* 2012, 10, 881–889. [CrossRef] [PubMed]

16. Song, Y.; Yang, R.C.; Xiao, Q.; Ju, Y. An efficient approach for the synthesis of 1′-O-α-methyl pyrrolo[2,3-d]pyrimidine isonucleosides. *Synthesis* 2011, 8, 1213–1218.

17. Dou, Y.H.; Ding, H.X.; Xiao, Q. A total synthesis of mycalisine A. *Chin. Chem. Lett.* 2013, 24, 379–382. [CrossRef]

18. Schram, K.H.; Townsend, L.B. Pyrrolopyrimidine nucleosides. Part XI. Influence of amino-groups at C-4 and C-6 or an amino-group at C-6 on the reactivity of a 5-cyano-group in pyrrolo[2,3-d] pyrimidine nucleosides. *J. Chem. Soc. Perkin Trans. 1* 1975, 1253–1257. [CrossRef]

19. Chung, F.L.; Schram, K.H.; Panzica, R.P.; Earl, R.A.; Wotring, L.L.; Townsend, L.B. Synthesis of certain [6:5:6] linear tricyclic nucleosides as potential antitumor agents. *J. Med. Chem.* 1980, 23, 1158–1166. [CrossRef] [PubMed]

20. Zhou, L.H.; Amblard, F.; Zhang, H.W.; McBrayer, T.R.; Detorrio, M.A.; Whitaker, T.; Coats, S.J.; Schinazi, R.F. Synthesis and evaluation of Janus type nucleosides as potential HCV NS5B polymerase inhibitors. *Bioorg. Med. Chem. Lett.* 2013, 23, 3385–3388. [CrossRef] [PubMed]

21. Moussodia, R.O.; Acherar, S.; Bordessa, A.; Vanderesse, R.; Jamart-Gregoire, B. An expedient and short synthesis of chiral α-hydrazinoesters: Synthesis and conformational analysis of 1:1 [α/α-Nα-hydrazino] mers. *Tetrahedron* 2012, 68, 4682–4692. [CrossRef]

22. Kavoosi, S.; Rayala, R.; Walsh, B.; Barrios, M.; Gonzalez, W.G.; Mikovska, J.; Mathivathanan, L.; Raptis, R.G.; Wnuik, S.F. Synthesis of 8-(1, 2, 3-triazol-1-yl)-7-deazapurine nucleosides by azide–alkyne click reactions and direct C-H bond functionalization. *Tetrahedron Lett.* 2016, 57, 4364–4367. [CrossRef] [PubMed]

23. Sabat, N.; Postova Slavetinska, L.; Klepetarova, B.; Hocek, M. C–H Phosphonation of pyrrolopyrimidines: synthesis of substituted 7-and 9-deazapurine-8-phosphonate derivatives. *J. Org. Chem.* 2016, 81, 9507–9514. [CrossRef] [PubMed]

24. Seela, F.; Peng, X.; Budow, S. Advances in the synthesis of 7-deazapurine-pyrrolo[2, 3-d]pyrimidine 2′-deoxyribonucleosides including D- and L-enantiomers, fluoro derivatives and 2,3′-dideoxyribonucleosides. *Curr. Org. Chem.* 2007, 11, 427–462. [CrossRef]

25. Crystallographic data for triciribine 1: C_{13}H_{16}N_{6}O_{4}, M = 374.37, crystal dimensions 0.26 × 0.28 × 0.30 mm, orthorhombic, space group, C2221 (No. 20). CCDC 1520825 contains the supplementary crystallographic data. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/date_request/cif.

**Sample Availability:** Samples of all the reported compounds are available from the Prof. Dr. Qiang Xiao.

© 2017 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).