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Synthesis of 2'(*R*)-Substituted Neplanocin A's (Nucleosides and Nucleotides. XXXVII¹)

Neplanocin A (I) was treated with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane to give 3',5'-*O*-(tetraisopropylidisiloxane-1,3-diyl)neplanocin A (II), which was converted to the 2'-*O*-trifluoromethanesulfonyl derivative (III). Nucleophilic substitution of III with a number of nucleophiles (AcO^- , AcS^- , N_3^- , Cl^- , Br^- , I^-) in hexamethylphosphoric triamide afforded the respective 2'(*R*)-substituted derivatives in high yield. The halogenated derivatives were reduced with tri-*n*-butyltin hydride to the 2'-deoxy compound. 2'-*O*-Thiocarbonylimidazolyl-3',5'-*O*-(tetraisopropylidisiloxane-1,3-diyl)neplanocin A was also reduced to the 2'-deoxy derivative. The deprotection of the bifunctional silyl group with tetra-*n*-butylammonium fluoride afforded 2'(*R*)-AcO, -AcS, - N_3 , -Cl, -Br, -I, and 2'-deoxy neplanocin A's, respectively. Physical data of these compounds including nuclear magnetic resonance, mass spectrum, and circular dichroism were given.

Keywords—neplanocin A; nucleoside antibiotic; nucleophilic substitution; triflate; tetra-*n*-butylammonium fluoride; NMR; MS; CD; protecting group

Neplanocin A (I) was isolated as a component of neplanocins from *Actinoplanacea ampullariella* sp., and showed a marked antitumor activity.²⁾ The structure of neplanocin A, 1-hydroxymethyl-3(*R*)-(adenin-9-yl)-4(*S*),5(*R*)-dihydroxycyclopent-1-ene, has been confirmed by nuclear magnetic resonance (NMR), mass spectrum (MS), ultraviolet (UV) and X-ray crystallography.³⁾ There has been considerable interests in the synthesis of 2'-modified nucleosides, stemming primarily from the antitumor or antiviral activities shown by

Chart 1

TABLE I. Physical Properties of 2'(R)-Substituted Neplanocin A's

Compd. No.	mp (°C)	Formula	Analysis(%)				Chemical shifts (δ)				MS (m/e)	CD[θ] ₂₅₂
			Calcd (Found)				$\overbrace{\text{H-1'} \quad \text{H-2'} \quad \text{H-6'}}^{(J_{1'2'})}$					
			C	H	N	X						
XII	195—197	C ₁₃ H ₁₅ N ₅ O ₄	51.14 (51.12)	4.95 4.98	22.94 22.74)		5.64 (d) (7Hz)	5.18 (dd)	5.80 (bs)		305(M ⁺) 245(M ⁺ —AcOH) 136(B+2)	—11900
XIII	165—167	C ₁₃ H ₁₅ N ₅ O ₃ ·1/2H ₂ O				X=S						
			47.26 (47.18)	4.88 4.94	21.20 21.58	9.70 9.61)	5.61 (d) (8Hz)	4.12 (dd)	5.80 (bs)		320(M ⁺ —1) 246(M ⁺ —SAc) 136(B+2)	—41800
XIV	239—240.5	C ₁₁ H ₁₃ N ₅ O ₃ ·1/3H ₂ O	49.13 (49.01)	5.00 5.01	26.04 25.97)		5.52 (d) (8Hz)	4.14 (dd)	5.72 (bs)		263(M ⁺) 136(B+2)	—9700
XV	231—233(dec.)	C ₁₁ H ₁₂ N ₈ O ₂	45.83 (45.86)	4.20 4.25	38.87 38.66)		5.64 (d) (8Hz)	4.27 (dd)	5.77 (bs)		288(M ⁺) 246(M ⁺ —N ₃) 136(B+2)	—19900
XVI	—	—	—	—	—	—	5.46 (d) (8Hz)	3.47 (dd)	5.71 (bs)		262(M ⁺) 136(B+2)	—10000
XVII	233—235(dec.)	C ₁₁ H ₁₂ ClN ₅ O ₂	46.90 (46.88)	4.29 4.32	24.86 24.79	X=Cl 12.59 12.51)	5.74 (d) (8Hz)	4.54 (dd)	5.86 (bs)		283,281(M ⁺) 246(M ⁺ —Cl) 136(B+2)	—11000
XVIII	224—226(dec.)	C ₁₁ H ₁₂ BrN ₅ O ₂	40.50 (40.57)	3.71 3.63	21.47 21.26	X=Br 24.50 24.24)	5.70 (d) (8Hz)	4.60 (dd)	5.86 (bs)		327,325(M ⁺) 246(M ⁺ —Br) 136(B+2)	—13000
XIX	212—215(dec.)	C ₁₁ H ₁₂ IN ₅ O ₂	35.40 (35.45)	3.24 3.28	18.77 19.13	X=I 34.01 33.02)	5.59 (d) (8Hz)	4.59 (dd)	5.84 (bs)		373(M ⁺) 246(M ⁺ —I) 136(B+2)	—19300
XX	231—234	C ₁₁ H ₁₃ N ₅ O ₂	53.43 (53.43)	5.30 5.25	28.33 28.04)		5.64 (m)	2.2—2.4 (m)	5.75 (bs)		247(M ⁺) 136(B+2)	—6900

arabinofuranosyl-cytosine (ara C) and -adenine (ara A).⁴⁾ It is well expected that the 2'-deoxy analog or 2'(*R*)-substituted derivatives of I may exhibit better chemotherapeutic indices than the original compound. For this purpose we have developed a synthetic route of the 2'(*R*)-substituted neplanocin A's.

Compound I was treated with 1,3-dichloro-1,1,3,3-tetraisopropylidisiloxane⁵⁾ in dimethylformamide to give a simultaneously protected derivative at the 3'- and 5'-hydroxyls, 3',5'-*O*-(tetraisopropylidisiloxane-1,3-diyl)neplanocin A (II), in 82% yield. In NMR spectrum of II, the 2'-hydroxyl proton appeared as doublet at δ 3.59 (disappears with addition of D₂O) and the 2'-proton appeared as triple doublet at δ 4.32 (collapsed to double doublet on addition of D₂O) which showed the protection had occurred between 5'- and 3'-hydroxyls. The X-ray analysis also confirmed⁶⁾ the structure of II. Treatment of II with trifluoromethanesulfonyl chloride and one equivalent of 4-dimethylaminopyridine in pyridine gave the 2'-*O*-triflate (III) in 89% yield. Nucleophilic displacement of III with a number of nucleophiles (NaOAc, KSAc, LiN₃, LiCl, LiBr, and LiI) were successful in hexamethylphosphoric triamide at room temperature for 1–20 hr to give the respective products (IV–IX). Deprotection of the bifunctional silyl group of IV and V with tetra-*n*-butylammonium fluoride in tetrahydrofuran proceeded at room temperature to afford XII and XIII, respectively. Deacetylation of XII gave ara-neplanocin A (XIV), an analog of ara A. De-silylation of VI followed by bubbling of H₂S into the aqueous solution of XV gave ninhydrin-positive 2'(*R*)-amino derivative (XVI), isolated as the amorphous acetate.

The reduction of VIII with tri-*n*-butyltin hydride in the presence of catalytic amount of azo-bis-isobutyronitrile in benzene afforded the 2'-deoxy derivative (X, MS 489 (M⁺), mp 149–151°) in 90% yield. In NMR spectrum of X, the 2'-protons appeared at δ 2.3–2.6 as octet, respectively. Compound X was prepared by an alternate route. Treatment of II with *N,N'*-thiocarbonyldiimidazole in refluxing 1,2-dichloroethane afforded a 2'-*O*-thiocarbonylimidazolyl derivative (XI). Reduction of XI with tri-*n*-butyltin hydride gave X in 61% isolated yield. Deprotection of X afforded 2'-deoxyneplanocin A (XX). The deprotection of VII–IX with tetra-*n*-butylammonium fluoride afforded the products (XVII–XIX), respectively, without affecting the *trans*-halohydrin system in these compounds.

The physical properties of the 2'(*R*)-substituted neplanocin A's prepared in this study are summarized in Table I. It should be noted that the bulkiness of the 2'-substituents affects strongly the molecular ellipticities, which may be based on the preference of anti-conformation around the "glycosyl" bond by the bulkier 2'(*R*)-substituents. In NMR spectra, coupling constants of the 1'-protons ($J_{1',2'}=8$ Hz) of these derivatives also reflected the (*R*)-configuration at the 2'-position, as compared with the $J_{1',2'}$ (5 Hz) of I.

Adenosine and other purine nucleosides could also be transformed to the varieties of 2'-modified 2'-deoxyarabinosylpurines by the similar procedure. The method described here has an advantage for the practical preparation of 2'-substituted nucleosides from ribonucleosides in general. The full details of the synthetic studies and results of the biological activities of these derivatives will be reported separately.

References and Notes

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