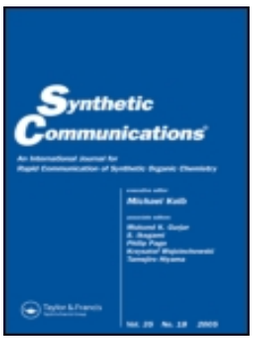


Taylor & Francis
Taylor & Francis Group

Synthetic Communications

An International Journal for Rapid Communication of Synthetic Organic Chemistry

ISSN: 0039-7911 (Print) 1532-2432 (Online) Journal homepage: http://www.tandfonline.com/loi/lsyc20

SYNTHESIS OF 1-(3',6'-ANHYDRO-2'-DEOXY- β-d-GLUCOFURANOSYL)-THYMINE

Hari Babu Mereyala & Pallavi Pola

To cite this article: Hari Babu Mereyala & Pallavi Pola (2002) SYNTHESIS OF 1-(3′,6′-ANHYDRO-2′-DEOXY- β-d-GLUCOFURANOSYL)-THYMINE, Synthetic Communications, 32:16, 2453-2458, DOI: 10.1081/SCC-120003393

To link to this article: http://dx.doi.org/10.1081/SCC-120003393

MARCEL DEKKER, INC. • 270 MADISON AVENUE • NEW YORK, NY 10016

SYNTHETIC COMMUNICATIONS
Vol. 32, No. 16, pp. 2453–2458, 2002

SYNTHESIS OF 1-(3′,6′-ANHYDRO-2′-DEOXY-β-D-GLUCOFURANOSYL)-THYMINE

Hari Babu Mereyala* **and Pallavi Pola**

Organic Chemistry Division III, Indian Institute of Chemical Technology, Hyderabad 500 007, India

ABSTRACT

Synthesis of bicyclic nucleoside **5** is described by coupling of **3** with *bis*(trimethylsilyl)thymine by use of Sn(IV)Cl as an activator. Synthesis of bicyclic 2′-deoxy analog **1** from **5** by radical deoxygenation of methylxanthate ester **6** is reported.

Synthesis of strained unusual oligonucleotides containing bicyclic nucleosides that form stable complexes with DNA and RNA gained enormous interest as they have been shown to be potent, but non-selective inhibitors of cyclic nucleotide phosphodiesterases.[1] Thus, 1,5-dioxabicyclo-[3.3.0]-octane believed to act as mimetic of ribose phosphate in cyclic nucleotides has been used as a template related to griseolic acid to design therapeutically useful compounds.[2] Bicyclic oligonucleosides have greater affinity for complementary RNA or DNA, C-3′ exo conformation is predictive of anti HIV activity.[3] Thus, bicyclic nucleoside analogues incorporating

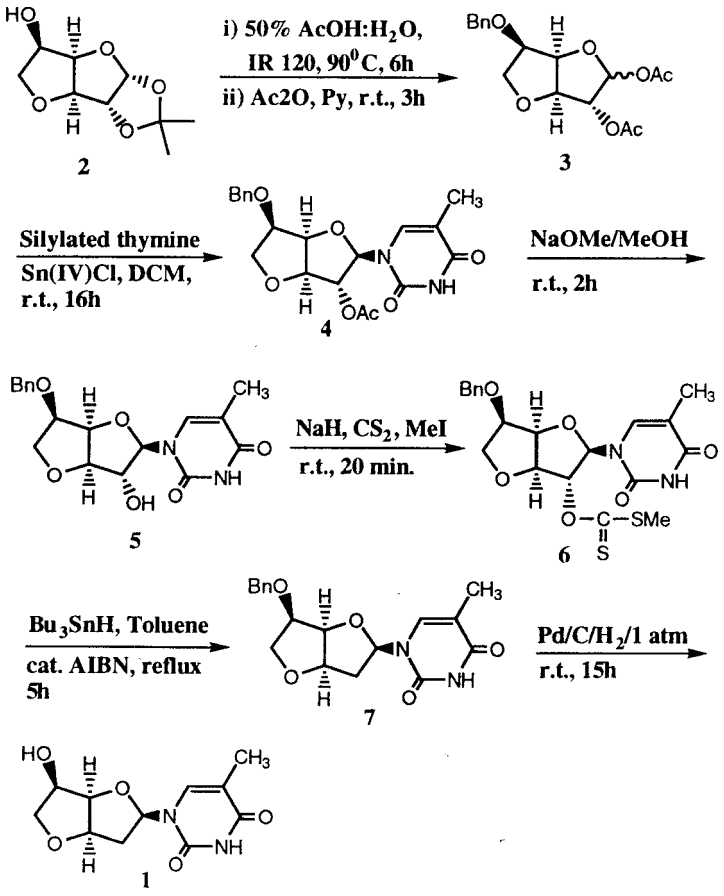
*Corresponding author. E-mail: haribabu@iict.ap.nic.in

DOI: 10.1081/SCC-120003393 0039-7911 (Print); 1532-2432 (Online)

fused methylene group,[4] oxirane,[5] oxetane[6] have been shown to inhibit HIV replication. Several bicyclic nucleosides have been earlier synthesised and tested for in vitro inhibitory effects on the replication of HIV-I.[7,8]

Due to our research programme directed towards synthesis of bicyclic nucleosides we have synthesised 1-(3′,6′-anhydro-2′-deoxy-β-D-glucofuranosyl)-thymine (**1**), as a potential antiviral compound (Scheme 1).

D-Glucose was transformed to 1,2-di-*O*-acetyl-3,6-anhydro-5-*O*-benzyl-α/β-D-glucofuranose (**3**) by literature described methods via 1,2-*O*-isopropylidene α-D-glucofuranose-5,6-carbonate[9] (**2**). Coupling of 1,2-di-*O*-acetyl-3,6-anhydro-5-*O*-benzyl-α/β-D-glucofuranose (**3**) with *bis*(trimethylsilyl)thymine was performed by use of Sn(IV)Cl as an activator at



Scheme 1.

room temperature to obtain the bicyclic nucleoside **4** in 70% yield.[10] **4** was characterised by ^{1}H NMR spectrum from the appearance of H-1′ at δ 6.15 (d, $J_{1',2'} = 5.0$ Hz) and 5-CH_3 at δ 1.80 as a singlet. **4** on reaction with a catalytic amount of NaOMe in methanol at room temperature gave 1-(3′,6′-anhydro-5′-*O*-benzyl-β-D-glucofuranosyl)-thymine (**5**) as a crystalline solid (m.p.: 158°C). **5** was characterised by ^{1}H NMR spectrum from the appearance of H-1′ at δ 5.85 as a singlet. Reaction of **5** with CS_2/NaH/MeI in dry THF at 0°C resulted in the formation of methyl xanthate ester **6** that on reduction with Bu_3SnH in toluene containing a catalytic amount of AIBN at reflux temperature gave 2′-deoxy bicyclic nucleoside **7** in good yield.[11] **7** was characterised from the ^{1}H NMR spectrum by the appearance of H-2′ protons at δ 2.30 (dd, $J_{2',2''} = 15.7$ Hz, $J_{1',2'} = 4.4$ Hz, H-2′), 2.65 (ddd, $J_{1',2''} = 6.75$ Hz, $J_{2'',3'} = 4.4$ Hz, H-2″) and H-1′ at δ 6.30 (dd, H-1′) as a multiplet. **7** on reductive debenzylation with 5% Pd/C at 1 atm hydrogen pressure gave **1** in good yield. **1** was characterised from ^{1}H NMR spectrum from the appearance of 5-CH_3 at δ 1.92 (s) and H-1′ at δ 6.45 (dd, $J_{1',2'} = 3.33$ Hz, $J_{1',2''} = 4.95$ Hz).

In conclusion, a general protocol for synthesis of novel bicyclic nucleosides **1** and **7** has been developed via the key bicyclic sugar derivative **3**. Applicability of this route for the synthesis of various bicyclic analogs of **1** and **7** is in progress.

EXPERIMENTAL SECTION

General Methods

Flame dried glassware, commercially available solvents and reagents were used without further purification unless otherwise stated. Melting points were measured using capillary tubes and are uncorrected. ^{1}H NMR spectra were measured with a Varian Gemini (200 MHz) spectrometer, with TMS as an internal standard using $CDCl_3$, as solvent. ^{13}C NMR spectra were taken with a Varian Gemini (50 MHz) spectrometer with solutions in deuterochloroform. Mass spectra were obtained on a VG 70-70H instrument.

1-(2′-*O*-Acetyl-3′,6′-anhydro-5′-*O*-benzyl-β-D-glucofuranosyl)-thymine (4): To a solution of 1,2-di-*O*-acetyl-3,6-anhydro-5-*O*-benzyl-α/β-D-glucofuranose (**3**) (0.5 g, 1.50 mmol) in dry CH_2Cl_2 (5 mL) was added *bis*(trimethylsilyl) thymine (0.5 g, 1.8 mmol) and $SnCl_4$ (0.1 mL) in CH_2Cl_2 (3 mL) under N_2 atmosphere. The reaction mixture was stirred at room temperature for 16 h. After completion of the reaction, the reaction mixture was diluted with CH_2Cl_2 (20 mL), neutralised with saturated aqueous $NaHCO_3$ solution

(5 mL) and filtered on a bed of celite. The filtrate was separated, added water (25 mL) and extracted the compound into CH_2Cl_2 (2 × 25 mL). The combined organic phase was dried (Na_2SO_4) and concentrated to obtain **4** (0.4 g, 69.5%) as a thick syrup. $[\alpha]_D + 97.2^\circ$(c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.80 (s, 3H, CH_3), 2.12 (s, 3H, $OCOCH_3$), 3.85–4.10 (m, 2H, H-6,6″), 4.21 (dt, 1H, $J_{4',5'} = J_{5',6'} = 4.8$ Hz, $J_{5',6''} = 4.5$ Hz, H-5′), 4.48 (dd, 1H, $J_{2',3'} = 1.5$ Hz, $J_{3',4'} = 4.0$ Hz, H-3′), 4.55 (d, 1H, $J = 12.5$ Hz, OCH_2Ph), 4.70 (d, 1H, OCH_2Ph), 4.75 (d, 1H, H-4′), 5.20 (dd, 1H, $J_{1',2'} = 4.0$ Hz, H-2′), 6.18 (d, 1H, H-1′), 7.30–7.45 (s, 5H, ArH), 7.50 (s, 1H, H-6), 8.50 (s, 1H, NH); FAB-MS: m/z 403 $(M+1)^+$, 425 $(M+23)^+$; Anal. Calcd. for $C_{20}H_{22}O_7N_2$ (402): C, 59.69; H, 5.51; N, 6.96%. Found: C, 59.52; H, 5.43; N, 6.87%.

1-(3′,6′-Anhydro-5′-*O*-benzyl-β-D-glucofuranosyl)-thymine (5): To a solution of **4** (0.4 g, 1 mmol) in CH_3OH (5 mL) was added NaOMe 1N (1.5 mL) and left the reaction mixture at room temperature for 2 h. The reaction mixture was neutralised with IR 120 H+, filtered and washed with methanol. The filtrate was concentrated to obtain **5** (0.3 g, 86%) as a white crystalline solid (m.p.: 158°C); $[\alpha]_D + 136^\circ$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.75 (s, 1H, CH_3), 3.80 (dd, 1H, $J_{6',6''} = 11.4$ Hz, $J_{5',6'} = 4.2$ Hz, H-6′), 3.98 (dd, 1H, $J_{5',6''} = 8.5$ Hz, H-6″), 4.40 (d, 1H, $J_{3',4'} = 2.8$ Hz, H-3′), 4.45 (s, 1H, H-2′), 4.48 (dd, 1H, $J_{4',5'} = 4.2$ Hz, H-4′), 4.55, 4.68 (dd, 2H, $J = 11.4$ Hz, 2 × OCH_2Ph), 5.06 (ddd, 1H, H-5′), 5.85 (s, 1H, H-1′), 7.29–7.41 (m, 5H, ArH), 8.02 (s, 1H, H-6), 10.08 (s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 17.2 (C-5), 72.2, 7.26 (C-6′, CH_2Ph), 79.6, 79.8, 82.2, 88.0 (C-2′,3′,4′,5′), 96.0 (C-1′), 110.0 (C-5), 127.8, 128.2, 136.4, 136.8 (Ar, C-6), 151.6 (C-2), 162.4 (C-4). Anal. Calcd. for $C_{18}H_{20}O_6N_2$. C, 59.99; H, 5.59; N, 7.77%. Found: C, 59.81; H, 5.48; N, 7.62%.

1-(3′,6′-Anhydro-5′-*O*-benzyl-2′-*O*-methylthiocarbonyloxy-β-D-glucofuranosyl)-thymine (6): To a solution of **5** (0.2 g, 0.6 mmol) in THF (5 mL) was added NaH (0.04 g, 1.7 mmol) and CS_2 (1 mL) at 0°C and stirred for 15 min. followed by addition of MeI (1 mL) at 0°C and stirred the reaction mixture at room temperature for 20 min. After completion of the reaction, chilled water (25 mL) was added and extracted the compound into EtOAc (2 × 25 mL). Combined organic layers were dried (Na_2SO_4) and concentrated to obtain a thick syrup which was filtered on a bed of SiO_2 (60–120 mesh) by eluting with EtOAc : hexane (1 : 1) to obtain the compound **6** (0.24 g, 91%) as a thick syrup. $[\alpha]_D + 70.3^\circ$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.84 (s, 3H, CH_3), 2.62 (s, 3H, SMe), 3.94 (dd, 1H, $J_{6',6''} = 10$ Hz, $J_{5',6'} = 5.0$ Hz, H-6′), 4.06 (dd, 1H, $J_{5',6''} = 7.0$ Hz, H-6″), 4.30 (dt, 1H, $J_{4',5'} = 5.0$ Hz, H-5′), 4.54 (d, 1H, $J = 12$ Hz, OCH_2Ph), 4.62 (d, 1H, $J_{3',4'} = 4.0$ Hz, H-3′), 4.74 (d, 1H, OCH_2Ph), 4.82 (dd, 1H, H-4′), 5.96 (d, 1H, $J_{1',2'} = 3.0$ Hz, H-2′), 6.31 (d, 1H, H-1′), 7.30–7.40 (s, 5H, ArH), 7.52 (s, 1H, H-6), 9.16 (s, 1H, NH). FABMS : m/z 451

$(M+1)^+$; Anal. Calcd. for $C_{20}H_{22}O_6N_2S_2$: C, 53.33; H, 4.92; N, 6.22%. Found: C, 53.11; H, 4.79; N, 6.11%.

1-(3′,6′-Anhydro-5′-*O*-benzyl-2′-deoxy-β-D-glucofuranosyl)-thymine (7): To a solution of **6** (0.2 g, 0.04 mmol) in distilled toluene (5 mL) was added Bu_3SnH (0.3 g, 1.2 mmol), a catalytic amount of AIBN and refluxed for 5 h under N_2 atmosphere. After completion of the reaction toluene was concentrated and the syrupy residue was chromatographed (SiO_2, 60–120 mesh) eluted with EtOAc : hexane (1 : 1) to obtain the title compound **7** (0.13 g, 72.0%) as a thick syrup. $[\alpha]_D + 108.4^\circ$ (c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.78 (s, 3H, CH_3), 2.30 (dd, 1H, $J_{2',2''} = 15.7$ Hz, $J_{1',2'} = 4.4$ Hz, H-2′), 2.65 (ddd, 1H, $J_{1',2''} = 6.75$ Hz, $J_{2'',3'} = 4.4$ Hz, H-2″), 3.80–4.00 (m, 2H, H-6′,6″), 4.28 (dt, 1H, $J_{4',5'} = J_{5',6''} = 6.75$ Hz, $J_{5',6'} = 9.0$ Hz, H-5′), 4.52 (d, 1H, $J = 11$ Hz, OCH_2Ph), 4.62 (2dd, 2H, $J_{3',4'} = 4.4$ Hz, H-3′,4′), 4.72 (d, 1H, OCH_2Ph), 6.30 (dd, 1H, H-1′), 7.30–7.40 (m, 5H, ArH), 7.82 (s, 1H, H-6), 8.45 (s, 1H, NH). FABMS: m/z 345 $(M+1)^+$, 367 $(M+23)^+$. Anal. Calcd. for $C_{18}H_{20}O_5N_2$: C, 62.78; H, 5.85; N, 8.14%. Found: C, 62.54; H, 5.76; N, 8.02%.

1-(3′,6′-Anhydro-2′-deoxy-β-D-glucofuranosyl)-thymine (1): To a solution of **7** (0.1 g, 0.2 mmol) in CH_3OH (10 mL) was added 5% Pd/C (5 mg) and hydrogenated (1 atm) for 16 h. After completion of the reaction the catalyst was filtered and washed with methanol. The filtrate was concentrated to obtain the title compound **1** (0.06 g, 83%) as a syrup. $[\alpha]_D + 22.80^\circ$(c 1.0, $CHCl_3$); ^{1}H NMR ($CDCl_3$): δ 1.92 (s, 1H, CH_3), 2.26 (dd, 1H, $J_{2',2''} = 15.5$ Hz, $J_{1',2'} = 4.95$ Hz, H-2′), 2.50–2.70 (m, 1H, H-2″), 3.85 (dd, 1H, $J_{6',6''} = 9.9$ Hz, $J_{5',6'} = 4.40$ Hz, H-6′), 4.00 (dd, 1H, $J_{5',6''} = 5.5$ Hz, H-6″), 4.35–4.80 (m, 3H, H-3′,4′,5′), 6.45 (dd, 1H, $J_{1',2''} = 3.33$ Hz, H-1′), 7.70 (s, 1H, H-6), 9.56 (s, 1H, NH); Anal. Calcd. for $C_{11}H_{14}O_5N_2$: C, 51.96; H, 5.55; N, 11.02%. Found: C, 51.71; H, 5.43; N, 10.93%.

ACKNOWLEDGMENT

PP thanks UGC-CSIR, New Delhi for financial support in the form of a Junior Research Fellowship.

REFERENCES

1. (a) Zamecnick, P.C.; Stephenson, M.L. Proc. Nat. Acad. Sci. USA **1978**, *75*, 280; (b) Stephenson, M.L.; Zamecnick, P.C. ibid **1978**, *75*, 285; c) Helene, C. Anti-cancer Drug Design **1991**, *6*, 569.
2. Nakagawa, F.; Okazaki, T.; Naito, A.; Iijima, Y.; Yamazaki, M. J. Antibiotics **1985**, *38*, 823.

3. (a) Van Roey, P.; Taylor, E.W.; Chu, C.K.; Schinazi, R.F. Ann. NY Acad. Sci. **1990**, *29*, 616; (b) Taylor, E.W.; Van Roey, P.; Schinazi, R.F.; Chu, C.K. Antiviral Chem. Chemother. **1990**, *1*, 163.
4. (a) Okabe, M.; Sun, R.C. Tetrahedron Lett. **1989**, *30*, 2203; (b) Beard, A.R.; Butler, P.I.; Mann, J.; Partlett, N.K. Carbohydr. Res. **1990**, *87*, 205.
5. Webb, T.R.; Mitsuya, H.; Broder, S.; J. Med. Chem. **1988**, *31*, 1475.
6. Counde, O.-Y.; Kurz, W.; Eugui, E.M.; McRoberts, M.J.; Verheyden, J.H.P.; Kurz, L.J.; Walker, K.A.M. Tetrahedron Lett. **1992**, *33*, 41.
7. Mitsuya, H.; Yarchoan, R.; Broder, S. Science **1990**, *249*, 1533.
8. Pineda Molas, M.; Isabel Matheu, M.; Sergio Castillon. Tetrahedron **1999**, *55*, 14649.
9. (a) Elmer, J.; Reist Roland, Spencer, R.; Baker, B.R. J. Org. Chem. **1958**, *23*, 1958; (b) Hall, L.D.; Hough, L. J. Chem. Soc. Perkin Trans. I **1963**, 5301.
10. Vorbruggen, H.; Hofle, G. Chem. Ber. **1981**, *114*, 1256.
11. Barton, D.H.R.; McCombie, S.W. J. Chem. Soc. Perkin Trans. I **1975**, 1574.

Received in the UK March 28, 2001