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A general and efficient route to 3′-deoxy-3′-*N*-, *S*-, and *C*-substituted altropyranosyl thymines from 2′,3′-*O*-anhydro-mannopyranosylthymine

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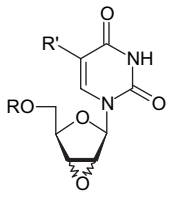
Abstract—An efficient route to 1-(2,3-*O*-anhydro-4,6-*O*-phenylmethylene-β-D-mannopyranosyl) thymine from 1,2,4,6-tetra-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranose has been devised. This newly synthesized epoxide is opened up regioselectively at the C-3′-position by *N*-, *S*-, and *C*-nucleophiles to afford a wide range of new 3′-deoxy-3′-substituted altropyranosyl thymines.

1. Introduction

The chemotherapeutic properties of dideoxynucleosides have triggered significant levels of interest in the synthesis and biological properties of pentofuranosyl nucleosides over the years.[1] However, the biological properties of several unnatural hexopyranosyl nucleosides were also recognized quite early. For example, 1-(2-deoxy-β-D-arabinohexopyranosyl) thymine,[2a,b] hexopyranosyl nucleosides derived from allose, altrose, gulose, talose, and mannose,[2c] 1-(2-deoxy-6-*O*-phosphono-β-D-ribohexopyranosyl)-2,4-pyrimidinedione,[2d] etc. have demonstrated interesting and varied biological properties. Synthetic studies on the pyranosyl nucleoside-based naturally occurring antibiotics have also been documented.[3] Furthermore, the syntheses and biological properties of a large number of pyranosyl azidonucleosides have been reviewed.[1] More recently, the syntheses and biological properties of a new class of sugar-modified nucleosides derived from 1,5-anhydrohexitols have been reported.[4] The syntheses of pyranose nucleosides and other nucleosides carrying tetrahydropyran structures have been reviewed.[5] However, all these reported methodologies are narrowly focused only to prepare special classes of compounds.[2–6] Surprisingly, no serious effort has been made so far to develop general methodologies for the synthesis of modified hexopyranosyl nucleosides from common intermediates as was the case for the pentofuranosyl nucleosides.[1,7] A full evaluation of the biological activity of differently substituted pyranose nucleosides will be possible only when they are easily accessible.

Nucleophilic ring-opening of 2′,3′-*O*-anhydro-uridine/lyxo-uridine and ribo-/lyxo-thymidine **1** and **2** in general is one of the most important strategies for the synthesis of sugar-modified nucleosides (Fig. 1).[1,7] The methodology has been used extensively for the synthesis of 2′/3′-amino-3′-deoxy-,[1,8] 2′/3′-thio-3′-deoxy-,[9] and 2′/3′-branched-3′-deoxy-[10] pentofuranosyl nucleosides. Considering the importance of hexopyranosyl nucleosides as 'new chemical entities' and in our quest for new methodologies for the synthesis of modified nucleosides,[8c,h,11] we envisaged that a functionalized compound like 2′,3′-*O*-anydro hexopyranosyl pyrimidine would have the potential to act as a versatile and general intermediate for the synthesis of modified hexopyranosyl pyrimidines. The selection of an epoxy nucleoside was also important because of the fact that 1-(2,4,6-tri-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranosyl) thymine (compound **11**, Scheme 2) although useful in producing various 3′-deoxy-3′-substituted allopyranosyl nucleosides,[11h] was incapable of reacting with a number of nucleophiles including amines and carbon nucleophiles because of the sluggish reactivity of C-3′ position on steric grounds.



1 R = H; **2** R = Me

Figure 1.

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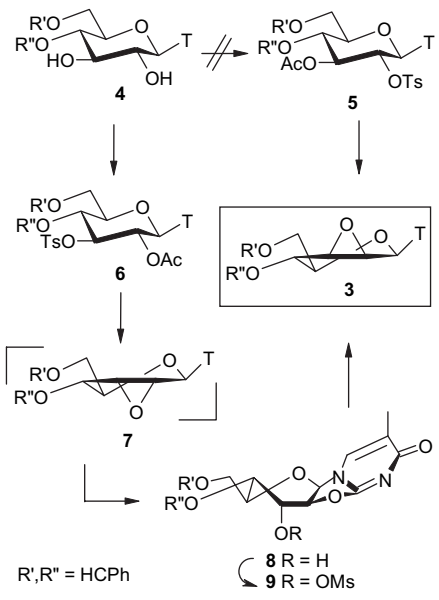
2. Results and discussion

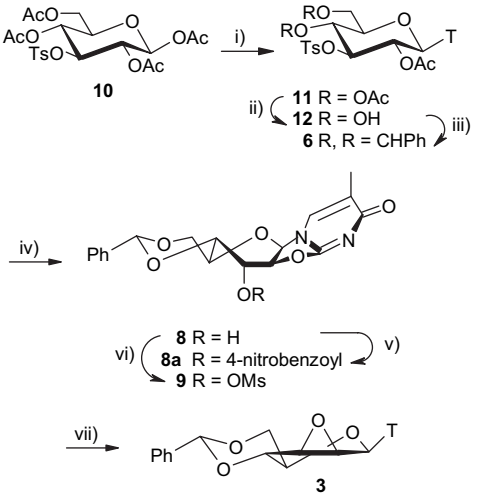
2.1. Synthesis of manno-epoxide 3

Although the epoxide ring-opening of nucleosides may appear to be an obvious strategy for the synthesis of modified hexopyranosyl nucleosides we were surprised to note that such compounds have not been exploited for the modification of sugar residues of these nucleosides. We planned to synthesize the benzylidene-protected manno-epoxide **3** (Scheme 1) because such compounds were known to undergo trans-diaxial type of attack of nucleophiles at C-3′ affording only altropyranosyl derivatives.[12] For the synthesis of manno-epoxide it would be necessary to selectively tosylate the C-2′ position of the partially protected diol **4** to get compound **5**. However, the reported selectivity of tosylation of the glucopyranosyl moiety of various nucleosides was confusing,[13–15] and the known report on the selective 3′-*O*-tosylation of methyl 4,6-*O*-benzylidene-β-D-glucopyranoside made use of equivalent amounts of dibutyltin oxide.[16] We wanted to avoid the use of highly toxic dibutyltin oxide in our large scale preparations and considered using pre-tosylated carbohydrates instead (see later) for coupling with the pyrimidine base to access directly 3′-*O*-tosylated nucleosides, such as **6**. Basic hydrolysis of **6** would produce allo-epoxide **7** but in the case of pyrimidine nucleosides, an intramolecular attack by the C-2 of the nucleobase at the C-2′ of the carbohydrate would open up the epoxide ring of **7** to produce the 2,2′-*O*-anhydro-derivative **8**. Compound **9**, easily produced from **8** would afford, under basic conditions manno-epoxide **3** (Scheme 1). The pattern of reaction sequences described here was well established in the case of epoxides derived from uridine.[7]



Scheme 1.

Our synthesis started with the easy conversion of 1,2:5,6-di-*O*-isopropylidene-3-*O*-*p*-toluenesulfonyl-α-D-glucofuranose[17] to 1,2,4,6-tetra-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranose **10** on large scale. Compound **10** was coupled with bistrimethylsilylated thymine to get the nucleoside **11** in good yield using a procedure reported for the coupling of nucleobases with pentaacetyl glucose (Scheme 2).[18] A large coupling constant for H1′–H2′ ($J_{1,2}$=9.5 Hz) indicated the β-configuration at C-1′ of **11**.[18] At this stage we were looking for an efficient method for the deacetylation of 4′- and 6′-*O*-acetyl groups retaining the 2′-*O*-acetyl protection. This was necessary because we did not want the deacetylated 2′-OH to attack intramolecularly the C-3′ position. Attempted deprotection using MeOH–NH_3 or MeOH–NaOMe produced an inseparable mixture of compounds. After several experiments, we identified MeOH–^{i}PrNH$_2$ as the best combination for the selective deacetylation of 4′- and 6′-*O*-acetyl groups to afford the diol **12**. Although the exact reason for this selective deacetylation was not clear to us, we argued that the presence of a controlled amount of amine (**11**:*iso*-propylamine=1:10) instead of a large excess of amine (for example, in saturated MeOH–NH_3) in the reaction mixture might have contributed to the selectivity. To establish the sites of deacetylation unambiguously, we directly converted crude **12** to the benzylidene-protected nucleoside **6** in an overall 70% yield over the two steps. This protecting group blocked the 4′- and 6′-hydroxyl groups and established the absence of any acetyl group on those two sites. Moreover, analytical and spectral data unambiguously established the structure of **6** and in turn that of **12** (Scheme 2).



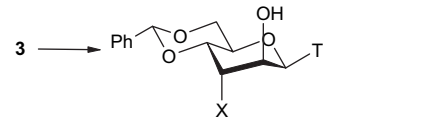
Scheme 2. Reagents and conditions: (i) 2,4-di-*O*-trimethylsilylthymine, $SnCl_4$, 1,2-dichloroethane, 50 °C, 75%; (ii) *iso*-propylamine, MeOH, rt, 5 h; (iii) $PhCH(OCH_3)_2$, TsOH, DMF, 100 °C, 1.5 h, 70% (from **11**); (iv) NaOMe, MeOH, rt, 30 h; (v) 4-nitrobenzoyl chloride, Py, rt, overnight; (vi) MsCl, Py, +4 °C, overnight; and (vii) 2 M NaOH, dioxane, rt, 0.5 h, 30–34% (from **6** to **3**).

Reaction of **6** with NaOMe/MeOH produced the highly hygroscopic material **8**, which was identified as its *p*-nitrobenzoyl derivative **8a** (see Section 4). Mesylation of **8** with mesyl chloride in pyridine at 0 °C afforded **9**. The crude mesylated product **9** was converted directly to 2′,3′-*O*-anhydro-mannopyranosyl nucleoside **3** by aqueous NaOH treatment in 30% overall yield over the three steps (Scheme 2).

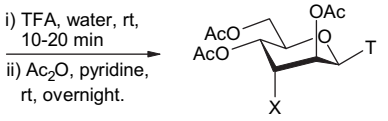
2.2. Reactions of manno-epoxide 3

To establish the synthetic utility of epoxide **3**, a range of nucleophiles was selected for opening the epoxide ring. Thus,

keeping in mind the importance of azido nucleosides,[1] **3** was reacted with a mixture of LiN_3 and NH_4Cl at elevated temperature in anhydrous ethanol to afford a single product **13a** containing the azido group. The product after purification was treated with TFA/water mixture (4:1) for a brief period to remove the phenylmethylene protecting group. However, for the convenience of isolation and purification the deprotected compound was acetylated to obtain **14a** in 65% (Scheme 3). This strategy of acetylation after deprotection was followed in all subsequent reactions with other nucleophiles. Since 2′-amino-2′-deoxythymidine was identified for its anti-HIV property in certain cell-lines,[1] and some of the 3′-*N*-alkylamino-3′-deoxy-ara-uridines[8c] were identified as potential inhibitors of ribonuclease A and angiogenin,[8h] we reacted **3** with a series of amines. Thus, *iso*-butylamine (70 °C for 24 h), pyrrolidine (90 °C for 24 h), morpholine (90 °C for 25 h), and 1-acetylpiperazine (90 °C for 30 h) opened the epoxide ring of **3** in DMSO to generate aminonucleosides **13b–e**, respectively. Imidazole also reacted with **3** at an elevated temperature to afford **13f**. The methodology was equally useful for the formation of a C–S bond at the C-3′ position. Thus, two thio-nucleophiles such as *p*-tolylthiol and NH_4SCN also opened the epoxide ring of **3** to generate thionucleosides **13g** and **13h**, respectively. To expand the scope of the methodology further, an important transformation was achieved by opening the epoxide ring of **3** with NaCN in DMF at elevated temperature to get **13i** (Scheme 3).[19] Compounds **13b–i** were converted to their triacetylated derivatives **14b–i**, respectively. As expected,[12] all epoxide opening reactions reported here generated single products. All products were identified as their triacetylated derivatives **14a–i**.

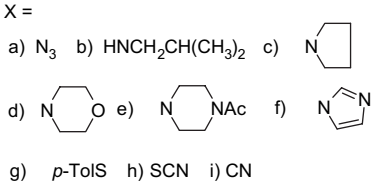


13a LiN_3, NH_4Cl, EtOH, reflux, 10 h (83%)
13b isobutylamine, DMSO 70 °C, 22 h (79%)
13c pyrrolidine, DMSO, 90 °C, 24 h (84%)
13d morpholine, DMSO, 90 °C, 25 h (80%)
13e 1-acetylpiperazine, 90 °C, 30 h (56%)
13f imidazole, TMG, DMSO, 70 °C, 20 h (86%)
13g TolSH, NaOMe, DMF, 70 °C, 10 h (66%)
13h NH_4SCN, DMF, 70 °C, 10 h (71%)
13i NaCN, DMF, 70 °C, 10 h (68%)



14a (65%); **14b** (70%); **14c** (85%)
14d (75%); **14e** (75%); **14f** (65%)
14g (55%); **14h** (56%); **14i** (65%)

X =



Scheme 3.

3. Conclusion

The strategy of coupling directly 1,2,4,6-tetra-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranose **10** with thymine, selective deacetylation of the product **11** and subsequent synthetic manipulations of **12** provided easy access to a versatile intermediate 1-(2,3-*O*-anhydro-4,6-*O*-phenylmethylene-β-D-mannopyranosyl) thymine **3**. This epoxy nucleoside reacted with azide, amines, sulfur nucleophiles as well as a carbon nucleophile paving the way for the synthesis of a great number and wide variety of hitherto unknown 3′-deoxy-3′-substituted-altropyranosyl thymines. It should be noted that these altropyranosyl nucleosides could not have been accessed by any other synthetic strategy. The biological properties of some of these compounds will be reported at a later date.

4. Experimental

4.1. General methods

All fine chemicals were obtained from commercial-suppliers and were used without purification. Solvents were dried and distilled following standard procedures. Melting points were determined in open-end capillary tubes using a Büchi B-540 electro-thermal melting point apparatus and are uncorrected. Analytical TLC was carried out on pre-coated aluminum plates (E-Merck silica gel 60, F_{254}) and spots were visualized with UV light or by charring the plate dipped in either 5% H_2SO_4–MeOH solution or ninhydrin solution in EtOH. Column chromatography was performed on silica gel (60–120 or 230–400 mesh). IR spectra were recorded as Nujol mull, or in solution (cond 1 μM) on a Shimadzu FTIR-8400 spectrophotometer. ^1H NMR was recorded at 200 MHz using AC 200 MHz, at 300 MHz using MSL 300 MHz, or 500 MHz using DRX 500 MHz in $CDCl_3$ using trimethylsilane as an internal standard. Special experiments such as ^1H–^1H COSY were carried out on 400 MHz at AV 400 MHz. ^{13}C-spectra and DEPT were recorded at 50.3, 75.5 or 125.8 MHz using the triplet centered at δ 77.0 as the standard. Specific rotations were determined using Bellingham ADP220 polarimeter or a JASCO P-1030 polarimeter at 589 nm. Mass spectral data were obtained using VG Analytical 70-250 AC normal geometry double focussing mass spectrometer, or Waters LCT mass spectrometer. Microanalytical data were obtained using a Carlo-Erba CHNS-0 EA 1108 Elemental analyzer.

4.1.1. 1-(2,4,6-Tri-*O*-acetyl-3-*O*-tosyl-β-D-glucopyranosyl) thymine 11. A mixture of thymine (2.52 g, 20 mmol), hexamethyldisilazane (15 mL), a few drops of trimethylsilyl chloride and a few crystals of $NH_4(SO_4)_2$ was heated under reflux for 3–5 h to get a clear solution. After cooling the moisture-sensitive reaction mixture to rt, volatiles were evaporated under reduced pressure. A solution of **10** (5.02 g, 10 mmol) in anhydrous 1,2-dichloroethane (60 mL) was added to the flask. Tin(IV) chloride (1.64 mL, 14 mmol) was injected in the flask with care. The reaction was allowed to stir at 50 °C. After 18 h the reaction mixture was cooled to rt. The reaction mixture was carefully poured into saturated $NaHCO_3$ solution (150 mL) and the products were extracted with chloroform (3×75 mL). Any emulsion formed was

filtered over a Celite bed and the bed was washed with chloroform (5×20 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered and the filtrate was concentrated under reduced pressure. The crude product was purified over silica gel column to afford **11** (4.25 g, 75%). Eluent: EtOAc/petroleum ether (2:3). White solid. Mp: 123–125 °C. $[\alpha]_D^{27}$ +16.7 (*c* 1.0, $CHCl_3$). IR (Nujol): 1749, 1693 cm^{-1}. ^1H NMR (^1H–^1H COSY) ($CDCl_3$): δ 1.87 (s, 3H, CH_3), 1.94 (s, 3H, thymine CH_3), 2.01 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.43 (s, 3H, CH_3), 3.90–3.93 (m, 1H, H5′), 4.11 (dd, *J*=2.0, 12.8 Hz, 1H, H6″), 4.27 (dd, *J*=5.0, 12.8 Hz, 1H, H6′), 5.08 (apparent t, *J*=9.3 Hz, 1H, H3′), 5.18–5.24 (m, 2H, H2′, H4′), 5.88 (d, $J_{1,2}$=9.5 Hz, 1H, H_1'), 7.11 (s, 1H, H-6), 7.33 (d, *J*=8.3 Hz, 2H, aromatic), 7.71 (d, *J*=8.3 Hz, 2H, aromatic), 8.84 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 12.2, 20.0, 20.3, 20.4, 21.3, 61.6 (CH_2), 67.2, 68.8, 74.3, 79.4, 79.8, 112.0, 127.3, 129.7, 133.7, 134.4, 145.0, 150.5, 163.3, 169.2, and 170.2. Anal. Calcd for $C_{24}H_{28}N_2O_{12}S\cdot 1/2H_2O$: C, 49.91; H, 5.06. Found: C, 50.00; H, 5.28. MS: EI *m/z* 568 [$4M^+$], 443 [$100M^+$−thymine], 396 [$29M^+$−*O*-tosyl].

4.1.2. 1-(2-*O*-Acetyl-4,6-*O*-(phenylmethylene)-3-*O*-tosyl-β-D-glucopyranosyl) thymine 6. To a solution of compound **11** (4.0 g, 7.04 mmol) in anhydrous methanol (75 mL), was added *iso*-propylamine (4.15 g, 70.4 mmol). The reaction mixture was stirred at rt for 5 h and then evaporated to dryness to provide product **12**, which was used in the next step without further purification. To a solution of crude **12** in anhydrous DMF (35 mL), benzaldehyde dimethyl acetal (1.42 mL, 10 mmol) and *p*-toluenesulfonic acid (10–12 mg) were added. The reaction mixture was heated at 100 °C under vacuum for 1 h. DMF was evaporated to dryness. The residual reaction mixture was re-dissolved in EtOAc (150 mL) and washed with aqueous saturated $NaHCO_3$ solution (2×25 mL). The organic layer was evaporated and the residue was dried. The crude product was purified over silica gel column to get the desired product **6** (3.0 g, 70% from **11**). Eluent: EtOAc/petroleum ether (1:1). White needles. Mp: 168–170 °C. $[\alpha]_D^{26}$ −42.2 (*c* 1.52, $CHCl_3$). IR (Nujol): 1755, 1711, 1697 cm^{-1}. ^1H NMR (^1H–^1H COSY) ($CDCl_3$): δ 1.94 (s, 3H), 2.05 (s, 3H), 2.31 (s, 3H), 3.69–3.76 (m, 3H, H4′, H5′, H6′), 4.35–4.40 (m, 1H, H6″), 5.06–5.15 (m, 1H, H3′), 5.26 (apparent t, *J*=9.3 Hz, 1H, H2′), 5.40 (s, 1H), 5.93 (d, *J*=9.5 Hz, 1H, H1′), 7.00 (d, *J*=8.3 Hz, 2H), 7.11 (s, 1H), 7.31–7.40 (m, 5H, aromatic), 7.67 (d, *J*=8.3 Hz, 2H), 8.61 (s, 1H). ^{13}C NMR (DMSO-d_6): δ 12.3, 20.2, 21.3, 67.3, 67.6 (CH_2), 69.9, 76.8, 79.8, 100.6, 110.3, 126.2, 127.6, 128.1, 129.1, 129.9, 133.9, 136.5, 137.0, 144.9, 150.6, 154.7, 163.7, 169.2. Anal. Calcd for $C_{27}H_{28}N_2O_{10}S\cdot 1/4H_2O$: C, 56.19; H, 4.98. Found: C, 56.20; H, 5.25. HRMS (ES^+): *m/z* calculated for $C_{27}H_{29}N_2O_{10}S$ $[M+H]^+$: 573.1543; found: 573.1517.

4.1.3. 2,2′-*O*-Anhydro-1-(4,6-*O*-phenylmethylene-β-D-altropyranosyl) thymine 8. A solution of compound **6** (1.9 g, 3.32 mmol) in anhydrous methanol (60 mL) was treated with sodium methoxide (0.91 g, 16.5 mmol) at rt. After 30 h the solution was neutralized with Dowex (50×8) H^+ resin. The reaction mixture was filtered and the filtrate was concentrated to dryness under reduced pressure. Hygroscopic **8** was dried by coevaporation with pyridine and taken on directly for next reactions.

4.1.4. 2,2′-*O*-Anhydro-1-(3-*O*-4-nitrobenzoyl-4,6-*O*-phenylmethylene-β-D-altropyranosyl) thymine 8a. To a solution of compound **8** (0.13 g, 0.36 mmol) in pyridine (7 mL) was added 4-nitrobenzoyl chloride (0.34 g, 1.85 mmol) at rt. The reaction mixture was stirred overnight. The reaction mixture was diluted with CH_2Cl_2 (75 mL) and washed with saturated $NaHCO_3$ solution (2×15 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated to obtain a residue. The crude product was purified on flash silica gel column to get the desired 4-nitrobenzoyl derivative **8a** (0.11 g, 62%; overall yield from **6**). Eluent: EtOAc/petroleum ether (4:1). Pale yellow solid. Mp: >300 °C. $[\alpha]_D^{26}$ −32.6 (*c* 0.35, DMF). IR (Nujol): 1742, 1676 cm^{-1}. ^1H NMR (CD_2Cl_2): δ 1.91 (s, 3H), 3.69 (t, *J*=10.3 Hz, 1H), 4.08–4.19 (m, 2H), 4.36 (dd, *J*=3.7, 9.5 Hz, 1H), 4.83 (s, 1H), 5.58 (s, 1H), 5.83 (d, *J*=3.6 Hz, 1H), 6.08 (s, 1H), 7.23–7.31 (m, 6H, aromatic), 8.23 (d, *J*=8.8 Hz, 2H), 8.30 (d, *J*=8.8 Hz, 2H). ^{13}C NMR (CD_2Cl_2): δ 14.2, 62.7, 66.6, 69.0 (CH_2), 74.0, 78.2, 82.8, 102.7, 120.5, 124.4, 126.6, 128.8, 129.8, 131.1, 131.6, 134.8, 137.3, 151.8, 160.3, 180.6. Anal. Calcd for $C_{25}H_{21}N_3O_9$: C, 59.17; H, 4.17. Found: C, 58.95; H, 4.09. MS: EI *m/z* 507 [$100M^+$].

4.1.5. 1-(2,3-*O*-Anhydro-4,6-*O*-phenylmethylene-β-D-mannopyranosyl) thymine 3. To a solution of **8** (obtained from 1.9 g/3.32 mmol of **6** as described above) in anhydrous pyridine (60 mL) was added methanesulfonyl chloride (1.70 mL, 21 mmol) at 0 °C. The reaction mixture was kept overnight at +4 °C. The solution was partitioned between saturated $NaHCO_3$ solution (30 mL) and $CHCl_3$ (30 mL). The aqueous phase was washed with $CHCl_3$ (3×30 mL). The combined organic layers were dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated to dryness under reduced pressure to obtain **9**. An aqueous solution of NaOH (2 M, 4.1 mL) was added drop-wise to a solution of crude **9** in dioxane (20 mL). The reaction mixture was stirred for 0.5 h at rt. EtOAc (50 mL) was added and the mixture was washed with saturated $NaHCO_3$ solution (2×15 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered, and the filtrate was concentrated to dryness. The residue was purified over silica gel to afford **3** (0.4 g, 34% from **6**). Eluent: EtOAc/petroleum ether (2:3). White needles. Mp: 255–257 °C. $[\alpha]_D^{29}$ +43.9 (*c* 1.1, $CHCl_3$). IR (Nujol): 1714, 1682 cm^{-1}. ^1H NMR (^1H–^1H COSY) ($CDCl_3$): δ 1.96 (s, 3H), 3.42 (d, *J*=3.8 Hz, 1H, H2′), 3.51–3.57 (m, 1H, H5′), 3.63 (d, *J*=3.7 Hz, 1H, H3′), 3.76–3.81 (m, 2H, H4′, H6′), 4.32 (dd, *J*=4.6, 10.5 Hz, 1H, H6″), 5.60 (s, 1H), 6.32 (s, 1H, H1′), 7.39–7.41 (m, 3H), 7.44 (s, 1H), 7.50–7.52 (m, 2H), 8.79 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.4, 50.5, 55.0, 68.8 (CH_2), 70.3, 74.1, 78.1, 102.6, 111.5, 126.1, 128.3, 129.3, 136.6, 150.6, 163.5. Anal. Calcd for $C_{18}H_{18}N_2O_6\cdot 1CHCl_3$: C, 47.77; H, 4.01. Found: C, 47.91; H, 4.18. MS: EI *m/z* 358 [$26M^+$], 233 [$4M^+$−thymine].

4.2. General method for the reaction of epoxide 3 with various nucleophiles

A mixture of epoxide **3** and the nucleophile in an appropriate solvent was heated until the epoxide disappeared (TLC). The mixture was cooled to rt and the volatiles were removed under reduced pressure. For **14a–e** and **14g–i**, the residue was diluted with EtOAc (50–75 mL) and for **14f** CH_2Cl_2

(50 mL) was used. The solution was successively washed with saturated $NaHCO_3$ solution (2×15 mL), water (10 mL), and brine (5 mL). The organic layer was dried over anhydrous Na_2SO_4 and filtered. The filtrate was evaporated to dryness and the solid residue was purified over silica gel to obtain a single compound **13a–i**. The product was treated with TFA/water mixture (4:1, 1 mL) at rt for up to 20 min (TLC). Solvents were evaporated and the residue was dried under reduced pressure. The residue was acetylated with acetic anhydride in dry pyridine at rt. Pyridine was evaporated under reduced pressure and the residue was dissolved in EtOAc (150 mL). The organic layer was washed with saturated $NaHCO_3$ solution (3×20 mL). The organic layer was separated, dried over anhydrous Na_2SO_4, and filtered. The filtrate was evaporated to dryness. The residue thus obtained was purified over silica gel to afford compounds **14a–i**.

4.2.1. 1-(2,4,6-Tri-*O*-acetyl-3-azido-β-D-altropyranosyl) thymine 14a. A mixture of epoxide **3** (0.36 g, 1.0 mmol), LiN_3 (0.490 g, 10.0 mmol), and NH_4Cl (0.27 g, 5.0 mmol) was heated under reflux in anhydrous EtOH (10 mL) for 10 h; **13a** (0.33 g, 83%), white solid; **14a** (0.25 g, 65%). Eluent: EtOAc/petroleum ether (2:3). White solid. Mp: 85–87 °C. $[\alpha]_D^{29}$ +55.1 (*c* 1.0, $CHCl_3$). IR ($CHCl_3$): 2115.8 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.93 (s, 3H), 2.09 (s, 3H), 2.12 (s, 3H), 2.17 (s, 3H), 4.23–4.37 (m, 4H), 5.14–5.17 (m, 2H), 6.02 (s, 1H), 7.23 (s, 1H), 9.27 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.5, 20.5, 20.6, 20.7, 59.0, 62.6 (CH_2), 66.0, 68.8, 73.0, 77.9, 110.3, 135.5, 149.5, 163.4, 168.8, 169.6, 170.6. Anal. Calcd for $C_{17}H_{21}N_5O_9$: C, 46.47; H, 4.82. Found: C, 46.34; H, 5.30. MS: ESI *m/z* 440.1 [100(M+H)$^+$], 314.1 [28(M+H)$^+$−thymine].

4.2.2. 1-(2,4,6-Tri-*O*-acetyl-3-*N*-isobutylamino-β-D-altropyranosyl) thymine 14b. A mixture of **3** (0.36 g, 1 mmol) and *iso*-butylamine (0.51 g, 7 mmol) in DMSO (5 mL) was heated at 70 °C for 24 h; **13b** (0.35 g, 79%), **14b** (0.26 g, 70%). Eluent: EtOAc/petroleum ether (3:2). White foam. Mp: 76–78 °C. $[\alpha]_D^{29}$ +78.9 (*c* 1.10, $CHCl_3$). IR ($CHCl_3$): 2958.6, 1745.5, 1691.5 cm^{-1}. ^1H NMR ($CDCl_3$): δ 0.93 (d, *J*=6.8 Hz, 3H), 0.97 (d, *J*=6.8 Hz, 3H), 1.73–1.75 (m, 1H), 1.93 (s, 3H), 2.07 (s, 3H), 2.11 (s, 3H), 2.12 (s, 3H), 2.50–2.53 (m, 2H), 3.26 (br s, 1H), 4.18–4.26 (m, 2H), 4.43–4.45 (m, 1H), 5.18 (br d, 1H), 5.23 (s, 1H), 6.35 (s, 1H), 7.30 (s, 1H), 8.32 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.4, 20.3, 20.4, 20.6, 20.7, 20.8, 28.5, 55.5 (CH_2), 56.7, 63.2 (CH_2), 66.5, 68.4, 72.8, 78.2, 109.8, 136.1, 149.5, 163.3, 169.2, 170.6. Anal. Calcd for $C_{21}H_{31}N_3O_9\cdot 1H_2O$: C, 51.74; H, 6.82. Found: C, 51.94; H, 6.41. MS: ESI *m/z* 470.2 [100(M+H)$^+$], 344.1 [22(M+H)$^+$−thymine].

4.2.3. 1-(2,4,6-Tri-*O*-acetyl-3-*N*-pyrrolidino-β-D-altropyranosyl) thymine 14c. A mixture of **3** (0.36 g, 1 mmol) and pyrrolidine (0.35 g, 5 mmol) in DMSO (3 mL) was heated at 90 °C for 24 h; **13b** (0.36 g, 84%), **14c** (0.33 g, 85%). Eluent: EtOAc/petroleum ether (3:2). White foam. Mp: 89–92 °C. $[\alpha]_D^{27}$ +68.3 (*c* 1.18, $CHCl_3$). IR ($CHCl_3$): 1743.5, 1687.6 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.76–1.79 (m, 4H), 1.93 (s, 3H), 2.07 (s, 3H), 2.09 (s, 3H), 2.11 (s, 3H), 2.72–2.73 (m, 2H), 2.79–2.80 (m, 2H), 2.92–2.93 (m, 1H), 4.25 (dd, *J*=2.0, 12.3 Hz, 1H), 4.32 (dd, *J*=5.9, 12.3 Hz, 1H), 4.59–4.61 (m, 1H), 5.27 (dd, *J*=2.8, 10.3 Hz, 1H), 5.45–5.46 (m, 1H), 6.25 (s, 1H), 7.31 (s, 1H), 8.38 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.5, 20.7, 21.1, 23.4 (CH_2), 52.7 (CH_2), 62.2, 63.1 (CH_2), 68.3, 69.6, 72.6, 78.2, 109.8, 136.0, 149.7, 163.5, 169.2, 169.5, 170.7. Anal. Calcd for $C_{21}H_{29}N_3O_9\cdot 1/2H_2O$: C, 52.94; H, 6.35. Found: C, 53.22; H, 6.48. MS: ESI *m/z* 468.2 [100(M+H)$^+$], 214.1 [32(M+H)$^+$−(thymine+3×CH_3CO)+H$^+$].

4.2.4. 1-(2,4,6-Tri-*O*-acetyl-3-*N*-morphino-β-D-altropyranosyl) thymine 14d. A mixture of **3** (0.36 g, 1 mmol) and morpholine (0.43 g, 5 mmol) in DMSO (4 mL) was heated at 90 °C for 25 h; **13d** (0.36 g, 80%), **14d** (0.29 g, 75%). Eluent: EtOAc/petroleum ether (3:2). White foam. Mp: 97–99 °C. $[\alpha]_D^{29}$ +37.1 (*c* 1.30, $CHCl_3$). IR ($CHCl_3$): 1745.5, 1689.5 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.94 (s, 3H), 2.06 (s, 3H), 2.13 (s, 6H), 2.67–2.78 (m, 4H), 2.98 (br s, 1H), 3.73 (br s, 4H), 4.25–4.34 (m, 2H), 4.38–4.41 (m, 1H), 5.33 (br d, 1H), 5.46 (br s, 1H), 6.23 (s, 1H), 7.27 (s, 1H), 8.80 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.4, 20.7, 21.1, 51.6 (CH_2), 62.0, 63.0 (CH_2), 67.1 (CH_2), 67.7, 74.9, 78.6, 109.9, 136.0, 149.7, 163.5, 169.2, 169.5, 170.6. Anal. Calcd for $C_{21}H_{29}N_3O_{10}\cdot 1/2H_2O$: C, 51.21; H, 6.14. Found: C, 51.09; H, 5.83. MS: ESI *m/z* 484.2 [100(M+H)$^+$], 358.1 [8(M+H)$^+$−thymine], 274.1 [31(M+H)$^+$−(thymine+2×CH_3CO)+2H$^+$].

4.2.5. 1-(2,4,6-Tri-*O*-acetyl-3-*N*-(1-acetylpiperazino)-β-D-altropyranosyl) thymine 14e. A mixture of epoxide **3** (0.36 g, 1 mmol) and 1-acetylpiperazine (0.64 g, 5 mmol) in DMSO (5 mL) was heated at 90 °C for 30 h; **13e** (0.28 g, 56%), **14e** (0.22 g, 75%). Eluent: EtOAc/petroleum ether (3:2). White foam. Mp: 105–107 °C. $[\alpha]_D^{29}$ +38.2 (*c* 0.60, $CHCl_3$). IR ($CHCl_3$): 1745.5, 1689.5, 1637.5 cm^{-1}. ^1H NMR (^1H–^1H COSY) ($CDCl_3$): δ 1.94 (s, 3H, thymine CH_3), 2.05 (s, 3H, CH_3), 2.08 (s, 3H, CH_3), 2.13 (s, 6H, 2×CH_3), 2.52–2.55 (m, 1H, piperazine), 2.68–2.83 (m, 3H, piperazine), 3.02 (dd, *J*=3.3, 4.1 Hz, 1H, H3′), 3.45–3.47 (m, 3H, piperazine), 3.74–3.78 (m, 1H, piperazine), 4.26–4.33 (m, 3H, H5′, H6′, H6″), 5.30 (dd, *J*=3.3, 5.5 Hz, 1H, H4′), 5.44 (dd, *J*=2.2, 5.1 Hz, 1H, H2′), 6.22 (d, $J_{1',2'}$=2.3 Hz, 1H, H1′), 7.27 (s, 1H, H-6), 9.28 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 12.4, 20.6, 20.7, 21.1, 41.6 (CH_2), 46.5 (CH_2), 50.9 (CH_2), 61.8, 63.0 (CH_2), 67.6, 67.8, 75.6, 78.7, 110.0, 135.9, 149.8, 163.5, 168.9, 169.2, 169.4, 170.5. Anal. Calcd for $C_{23}H_{32}N_4O_{10}\cdot 1H_2O$: C, 50.92; H, 6.35. Found: C, 50.76; H, 6.55. MS: ESI *m/z* 525.2 [100(M+H)$^+$].

4.2.6. 1-(2,4,6-Tri-*O*-acetyl-3-*N*-imidazoline-β-D-altropyranosyl) thymine 14f. 1,1,3,3-Tetramethylguanidine (0.17 g, 1.5 mmol) was added to a solution of imidazole (0.17 g, 2.5 mmol) in DMSO (2 mL). After 15 min at rt, the epoxide **3** (0.18 g, 0.5 mmol) was added to the solution. The reaction mixture was heated at 70 °C for 20 h; **13f** (0.18 g, 86%), **14f** (0.12, 65%). Eluent: EtOAc/petroleum ether (4:1). White solid. Mp: 108–110 °C. $[\alpha]_D^{27}$ +20.4 (*c* 1.47, $CHCl_3$). IR ($CHCl_3$): 1753.2, 1691.5 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.95 (s, 3H), 2.00 (s, 3H), 2.13 (s, 3H), 2.16 (s, 3H), 4.22–4.47 (m, 3H), 4.76 (dd, *J*=4.3, 5.8 Hz, 1H), 5.22 (dd, *J*=4.3, 5.9 Hz, 1H), 5.64 (dd, *J*=3.1, 5.5 Hz, 1H), 6.25 (d, *J*=3.2 Hz, 1H), 7.15 (br s, 2H), 7.23 (s, 1H), 7.70 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.4, 20.3, 20.7, 55.8, 62.9 (CH_2), 68.0, 69.1, 76.1, 78.8, 110.5, 118.5, 130.2, 135.2, 137.3, 149.7, 163.4, 168.7, 169.6, 170.4. Anal. Calcd

for $C_{20}H_{24}N_4O_9 \cdot 1/4H_2O$: C, 51.23; H, 5.27. Found: C, 51.31; H, 5.46. MS: ESI *m/z* 465.2 [100(M+H)$^+$].

4.2.7. 1-(2,4,6-Tri-*O*-acetyl-3-*S*-thio-(*p*)tolyl-β-D-altropyranosyl) thymine 14g. NaOMe (0.14 g, 2.5 mmol) was added to a solution of *p*-thiocresol (0.44 g, 3.5 mmol) in DMF (5 mL). After 15 min at rt, epoxide **3** (0.18 g, 0.5 mmol) was added to the solution. The reaction mixture was heated at 70 °C for 10 h; **13g** (0.16 g, 66%), **14g** (0.12 g, 55%). Eluent: EtOAc/petroleum ether (3:2). White needles. Mp: 77–82 °C. $[\alpha]_D^{25}$ +99.1 (*c* 1.29, $CHCl_3$). IR ($CHCl_3$): 1745.5, 1689.5 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.93 (s, 3H), 2.01 (s, 3H), 2.03 (s, 3H), 2.13 (s, 3H), 2.33 (s, 3H), 4.00–4.04 (m, 1H), 4.29–4.44 (m, 3H), 5.11–5.18 (m, 2H), 6.49 (d, *J*=1.6 Hz, 1H), 7.15 (d, 2H), 7.27 (s, 1H), 7.44 (d, 2H), 8.72 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 12.5, 20.7, 20.8, 21.1, 49.5, 62.9 (CH_2), 65.9, 70.1, 73.8, 78.0, 110.0, 127.5, 130.2, 134.0, 135.9, 138.9, 149.5, 163.5, 168.9, 169.7, 170.7. Anal. Calcd for $C_{24}H_{28}N_2O_9S \cdot 1/4H_2O$: C, 54.90; H, 5.47. Found: C, 54.77; H, 5.40. MS: ESI *m/z* 521.1 [100(M+H)$^+$], 461.1 [43(M+H)$^+$−CH_3CO_2H], 395.1 [28(M+H)$^+$−thymine], 275.1 [25(M+H)$^+$−(thymine+2×CH_3CO_2H)].

4.2.8. 1-(2,4,6-Tri-*O*-acetyl-3-*S*-thionitrilo-β-D-altropyranosyl) thymine 14h. A mixture of epoxide **3** (0.36 g, 1 mmol) and NH_4SCN (0.36 g, 5 mmol) in DMF (3 mL) was heated at 70 °C for 5 h; **13h** (0.3 g, 71%), **14h** (0.18 g, 56%). Eluent: EtOAc/petroleum ether (1:1). White foam. Mp: 89–90 °C. $[\alpha]_D^{25}$ +65.0 (*c* 1.40, $CHCl_3$). IR ($CHCl_3$): 2164 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.94 (s, 3H), 2.12 (s, 3H), 2.14 (s, 3H), 2.20 (s, 3H), 4.23–4.42 (m, 4H), 5.30 (dd, 1H), 5.43–5.45 (m, 1H), 6.01 (d, *J*=1.5 Hz, 1H), 7.21 (s, 1H), 8.93 (s, 1H). ^{13}CNMR ($CDCl_3$): δ 12.4, 20.3, 20.4, 20.6, 48.5, 62.2 (CH_2), 64.5, 68.8, 73.9, 77.8, 108.8, 110.5, 135.0, 149.6, 163.5, 168.5, 169.3, 170.4. Anal. Calcd for $C_{18}H_{21}N_3O_9S$: C, 47.47; H, 4.65. Found: C, 47.77; H, 4.64. MS: ESI *m/z* 456.1 [100(M+H)$^+$], 414.1 [22(M+H)$^+$−CH_3CO+H$^+$], 330.1 [38(M+H)$^+$−thymine].

4.2.9. 1-(2,4,6-Tri-*O*-acetyl-3-cyano-β-D-altropyranosyl) thymine 14i. A mixture of epoxide **3** (0.18 g, 0.5 mmol) and NaCN (0.12 g, 2.5 mmol) in DMSO (2 mL) was heated at 70 °C for 10 h; **13i** (0.14 g, 68%), **14i** (0.10 g, 65%). Eluent: EtOAc/petroleum ether (2:3). White solid. Mp: 99 °C. $[\alpha]_D^{25}$ +64.5 (*c* 0.78, $CHCl_3$). IR ($CHCl_3$): 2254.6 cm^{-1}. ^{1}H NMR (^{1}H–^{1}H COSY) ($CDCl_3$): δ 1.93 (s, 3H, thymine CH_3), 2.12 (s, 3H, CH_3), 2.14 (s, 3H, CH_3), 2.19 (s, 3H, CH_3), 3.56 (dd, *J*=2.8, 11.1 Hz, 1H, H3′), 3.96−3.98 (m, 1H, H5′), 4.19 (dd, *J*=2.5, 12.5 Hz, 1H, H6′), 4.32 (dd, *J*=6.0, 12.5 Hz, 1H, H6″), 5.39 (apparent t, *J*=10.1 Hz, 1H, H4′), 5.70 (m, 1H, H2′), 5.87 (d, *J*=1.3 Hz, 1H, H1′), 7.19 (s, 1H, H-6), 9.77 (br s, 1H, NH). ^{13}C NMR ($CDCl_3$): δ 12.5, 20.3, 20.5, 20.7, 36.6, 62.1 (CH_2), 63.5, 66.1, 77.3, 80.5, 111.0, 115.0, 134.4, 149.9, 163.3, 168.9, 169.2, 170.5. Anal. Calcd for $C_{18}H_{21}N_3O_9 \cdot 1/2H_2O$: C, 50.00; H, 5.13. Found: C, 50.23; H, 5.20. MS: ESI *m/z* 424.1 [100(M+H)$^+$], 382.1 [35(M+H)$^+$−CH_3CO+H$^+$], 298.1 [51(M+H)$^+$−thymine].

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