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2-(*tert*-Butyldimethylsiloxy)thiophene: Application to Total Syntheses of Both Enantiomers of 2',3'-Dideoxy-4'-thiocytidine

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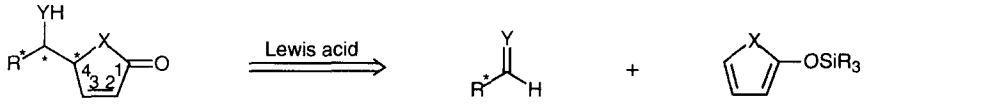
Abstract: Exploiting novel 2-(*tert*-butyldimethylsiloxy)thiophene (**1**, TBSOT) as versatile carbon nucleophile and both enantiomers of glyceraldehyde acetonide as chiral sources, an entry to both enantiomers of anti HIV-active 2',3'-dideoxy-4'-thiocytidine **10** and *ent*-**10** was devised and executed.

Enantiomerically pure units of type **A** are attractive heterocycles and valuable building blocks for syntheses of a myriad of biologically interesting compounds bearing diverse functionality and multiple chirality. The α,β-unsaturated moiety within **A** can be hydrogenated, dihydroxylated, or utilized as a Michael acceptor, while the C-2 carbon is susceptible to electrophilic substitution. 1,2-Addition to the C-1 carbonyl can be effected under a variety of conditions, whereas alkylation at C-4 can be carried out via the enolate. Due to its chiral nature, the C-4 substituent provides a configurational bias to be used to control the stereochemical outcome of the various functionalization processes.



Aa : X = O
Ab : X = NBoc
Ac : X = S

Ba : Y = O
Bb : Y = NR

TMSOF : X = O; R_3 = Me_3
TBSOP : X = NBoc; R_3 = Bu^tMe_2
TBSOT : X = S; R_3 = Bu^tMe_2

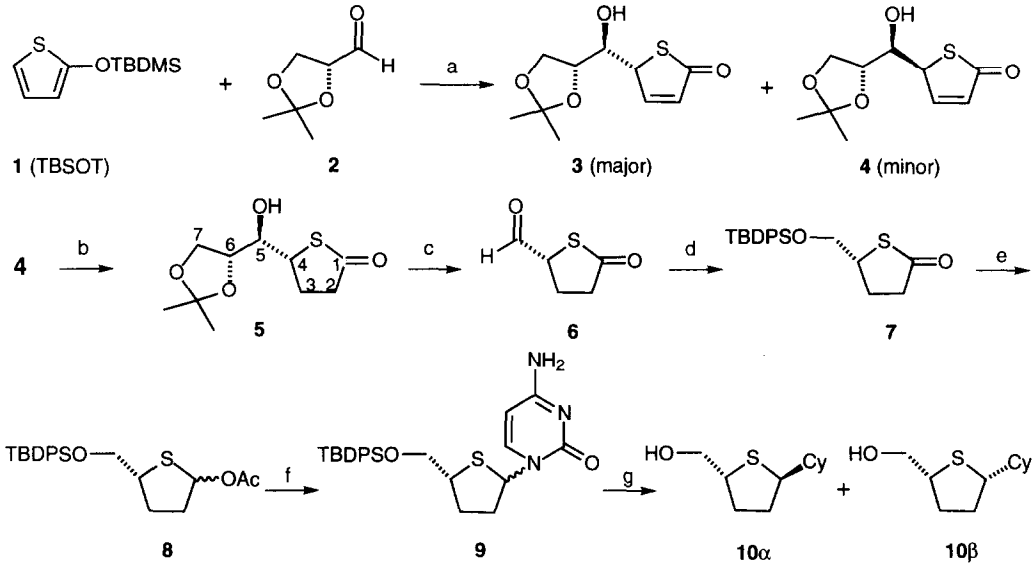
In addition to these useful synthetic implications, lactones **Aa** or lactams **Ab** are readily accessible, in a single sequence, via Lewis acid-assisted diastereoselective coupling of homochiral aldehyde **Ba** or imine **Bb** precursors by means of 2-(trimethylsiloxy)furan (TMSOF) or *N*-*tert*-butoxycarbonyl-2-(*tert*-butyldimethylsiloxy)pyrrole (TBSOP), respectively.[1-4] We have reported that furan- and pyrrole-based compounds **Aa** and **Ab** serve as chiral templates for the stereoselective preparation of densely functionalized bioactive compounds including higher carbon sugars,[1] polyhydroxylated alkaloids,[2] *C*-glycosyl-α-amino acids,[3] and azasugar-based nucleosides.[4]

Because of the excellent potential of sulfur modified sugars and nucleosides in a broad range of synthetic and biological applications,[5] it seemed desirable and pertinent to develop a clean, synthetically efficient method for the production of thiolactone intermediates of type **Ac** in enantiomerically pure forms. We have now achieved this objective and report herein the first access to 2-(*tert*-butyldimethylsiloxy)thiophene (**1**, TBSOT) and its exploitation to preparation of thiolactones of type **3** and **4**

and expedient syntheses of both enantiomers of anti-HIV active 2',3'-dideoxy-4'-thiocytidine **10** and *ent*-**10**.[5c]

Our strategy for the synthesis of the key enantiomeric thiofuranose precursors **8** and *ent*-**8** relies upon Lewis acid promoted addition of TBSOT to glyceraldehyde derivatives **2** and *ent*-**2** to produce the diastereomeric α,β-unsaturated adducts **3**, **4** and *ent*-**3**, *ent*-**4**. Double bond saturation followed by oxidative extrusion of the C-6 and C-7 carbon atoms and reduction of the C-1 thiolactone carbonyl should then lead to **8** and *ent*-**8**, to be finally subjected to conventional coupling with the suitable nucleobase.

Scheme 1



Reagents: a) TBSOT, BF_3 etherate (1.0 equiv), CH_2Cl_2, -90°C, 5h; b) H_2, 10% Pd on carbon, NaOAc, THF, 20°C, 12h; c) 80% aq. AcOH, 40°C, 24h; then 0.65M aq. $NaIO_4$, SiO_2, CH_2Cl_2, 22°C, 1h; d) $NaBH_4$, MeOH, 25°C, 12h; then TBDPS-Cl, imidazole, DMF, 25°C, 2h; e) $LiAlH_4$ (0.5 equiv), THF, -20°C, 7h; then Ac_2O, pyridine, DMAP, 25°C, 2h; f) cytosine (1.5 equiv), nonafluorobutanesulfonate, CH_3CN, HMDS, TMS-Cl, 25°C, 24h; g) preparative TLC, SiO_2, $CHCl_3$/MeOH (9:1) in NH_3 atmosphere; then TBAF, THF, AcOH, 25°C, 20h.

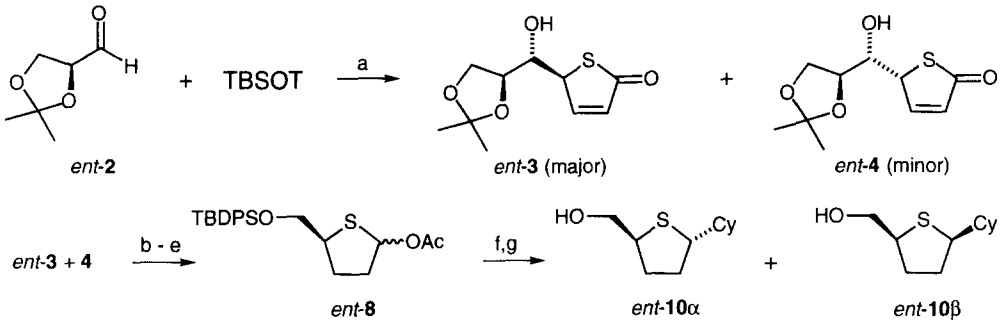
As depicted in Scheme 1, the synthesis of cytidine derivatives **10** (L-series) started from TBSOT and 2,3-*O*-isopropilydene-D-glyceraldehyde **2**. Silyl-dienol ether formation to produce stable TBSOT was cleanly effected (95%) from commercially available 2(5H)-thiophenone by following a well-tried *tert*-butyldimethylsilyltrifluoromethanesulfonate/2,6-lutidine-based protocol.[2a,6] Diastereoselective addition of TBSOT to **2** in the presence of 1.0 equiv of BF_3 etherate in CH_2Cl_2 resulted in preferential formation of the 4*R*-adduct **3** (72%) accompanied by less than 10% of 4*S*-diastereoisomer **4**. Hydrogenation of the major compound **3** (10% Pd on carbon, THF, NaOAc) furnished crystalline thiolactone **5** (88%), whose absolute (4*R*,5*R*,6*R*)-configuration was unambiguously ascertained by single crystal X-ray analysis.[7] This confirmed the prediction that the major coupling product **3** would have the 4,5-*threo*-5,6-*erythro*- configuration, indicative of a reactivity behavior similar to that observed for furan- and pyrrole-based siloxydienes.[1-4]

Selective deblocking of the acetonide protection within **5** (80% aq. AcOH), followed by exposure of the formed crude triol to $NaIO_4/SiO_2$ in CH_2Cl_2, cleanly afforded aldehyde **6** (91%), which was used as such in the subsequent transformation. Reduction of the formyl moiety of **6** ($NaBH_4$/MeOH) and subsequent silylation of the created primary hydroxyl function with *tert*-butyldiphenylsilyl chloride (TBDPS-Cl, imidazole, DMF) then gave **7**, the immediate precursor of thiosugar **8**, in 77% yield.

Selective reduction of thiolactone carbonyl to thiolactol was attained by careful exposure of **7** to $LiAlH_4$ (0.5 equiv) in tetrahydrofuran at -20°C. No reaction occurred under standard conditions with either DIBAL-H or $LiBEt_3H$ reducing agents. Following acetylation of the anomeric hydroxyl (Ac_2O, pyridine, DMAP) pure L-thiofuranose **8** was obtained, as a 1:1 anomeric mixture, in 82% yield, which corresponds to a 37% overall yield based on **2**. The final coupling of **8** with cytosine was successfully conducted according to a modification of the Vorbruggen protocol,[8] by following exactly the experimental procedure of Secrist.[5c] In our hands, the reaction afforded a 68% yield of **9** as a 1:1 α/β anomeric mixture. The separation of the individual anomers was carried out by preparative TLC (AcOEt/MeOH 9:1 in ammonia atmosphere) allowing synthesis of pure nucleoside anomers **10**α and **10**β.[9,10]

The synthesis of known anti-HIV active 4'-thiocytidine *ent*-**10**[5c] (D-series) called for thiosugar *ent*-**8** as immediate precursor. It was envisaged that transformation of either the minor adduct **4** (from D-glyceraldehyde **2**), or the major adduct *ent*-**3** (from L-glyceraldehyde *ent*-**2**) would provide this key intermediate by the same operational sequence. Thus, as described for **3**, crystalline *ent*-**3** was prepared by reacting TBSOT with *ent*-**2** (73% isolated yield), and conveniently combined with **4**, thus minimizing loss of homochiral material (Scheme 2).

Scheme 2



Reagents: See Scheme 1.

The same set of reactions as described for **8** then allowed this diastereoisomeric mixture (*dr* = 80:20) to be elaborated into the sole enantiomer *ent*-**8** in 50% overall yield based on *ent*-**3,4** mixture. Final coupling of *ent*-**8** with cytosine was carried out in the usual manner[5c] to obtain a mixture of protected nucleosides (65%, 1:1 α,β anomeric ratio), from which the pure semicrystalline β-anomer of 2',3'-dideoxy-4'-thiocytidine (*ent*-**10**β) was obtained as previously described for its enantiomer **10**β [mp 81-83°C; lit.[5c] mp 83-85°C].

In conclusion, utilizing readily available D- and L-glyceraldehyde acetonides as a couple of "enantiomeric" hydroxymethyl (or formyl) cation equivalents, a flexible route to enantiomerically pure thiofuranose-based nucleosides was devised and straightforwardly executed. Novel TBSOT and previously

described TMSOF and TBSOP constitute a powerful triad of four-carbon nucleophiles whose application in synthesis is expected to be more and more fruitful.

Acknowledgment

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6. **1** (TBSOT): To a solution of 2(5H)-thiophenone (1.24 g, 12.4 mmol) in anhydrous CH_2Cl_2 (40 mL) were added 2,6-lutidine (4.3 mL) and TBDMS-OTf (4.25 g, 16.1 mmol) under argon at room temperature. After the reaction mixture was stirred for 30 min, the solvent was evaporated and the residue subjected to flash chromatographic purification on silica gel (1:1 EtOAc/hexanes) to furnish 2.5 g (95%) of **1** as a pale yellow oil; ^1H NMR (300 MHz, $CDCl_3$): δ = 6.62 (dd, 1H, J = 6.0, 3.6 Hz), 6.46 (dd, 1H, J = 6.0, 1.2 Hz), 6.11 (dd, 1H, J = 3.6, 1.2 Hz), 0.96 (s, 9H), 0.21 (s, 6H); ^{13}C NMR (75.2 MHz, $CDCl_3$) δ 150.8, 124.4, 112.7, 109.0, 25.6, 18.2, -5.0.
7. G. Gasparri Fava, M. Belicchi Ferrari, G. Pelosi, unpublished results.
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9. Assignment of the α- and β-anomeric configurations was based on NOE difference spectroscopy (300.13 MHz). For β-anomer irradiation of H-1' at 6.31 ppm gave enhancement of H-4', while this effect was not detected in the corresponding α-anomer (H-1' at 6.26 ppm).
10. **10α** and **10β** (5'-*O*-TBDPS derivatives):β-anomer, $[\alpha]_D^{20}$ = -43.8 (*c* 0.16, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 8.12 (d, 1H, J = 7.5 Hz, H-6), 7.69 (m, 4H, ArH), 7.44 (m, 6H, ArH), 6.31 (dd, 1H, J = 5.7, 3.0 Hz, H-1'), 5.48 (d, 1H, J = 7.5 Hz, H-5), 3.90 (dd, 1H, J = 10.5, 5.7 Hz, H-5'a), 3.81 (dd, 1H, J = 10.5, 5.4 Hz, H-5'b), 3.70 (m, 1H, H-4'), 2.30 (m, 1H, H-2'a), 2.09 (m, 2H, H_2-3'), 1.80 (m, 1H, H-2'b), 1.09 (s, 9H, Bu^t); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.7 (C-2), 156.1 (C-4), 143.4 (C-6), 135.7 (ArC_{ortho}), 133.1 (ArC-1), 129.9 (ArC_{para}), 127.8 (ArC_{meta}), 93.4 (C-5), 66.1 (C-1'), 65.7 (C-5'), 52.7 (C-4'), 38.0 (C-2'), 29.7 (C-3'), 26.9 (Bu^t), 19.3 (C-Bu^t). α-Anomer, $[\alpha]_D^{20}$ = -14.3 (*c* 0.20, $CHCl_3$) ^1H NMR (300 MHz, $CDCl_3$) δ 7.96 (d, 1H, J = 7.5 Hz, H-6), 7.66 (m, 4H, ArH), 7.41 (m, 6H, ArH), 6.26 (dd, 1H, J = 4.4, 2.0 Hz, H-1'), 5.96 (d, 1H, J = 6.9 Hz, H-5), 3.82 (m, 1H, H-4'), 3.63 (m, 2H, H_2-5'), 2.32 (m, 1H, H-2'a), 1.98 (m, 3H, H_2-3' and H-2'b), 1.06 (s, 9H, Bu^t); ^{13}C NMR (75.4 MHz, $CDCl_3$) δ 164.1 (C-2), 155.1 (C-4), 142.8 (C-6), 135.6 (ArC_{ortho}), 133.2 (ArC-1), 129.8 (ArC_{para}), 127.8 (ArC_{meta}), 94.4 (C-5), 66.7 (C-1'), 65.4 (C-5'), 51.5 (C-4'), 37.0 (C-2'), 29.9 (C-3'), 26.8 (Bu^t), 19.2 (Bu^tC).

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