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Stereocontrolled Syntheses of C-Linked Deoxyribosides of 2-Hydroxypyridine and 2-Hydroxyquinoline

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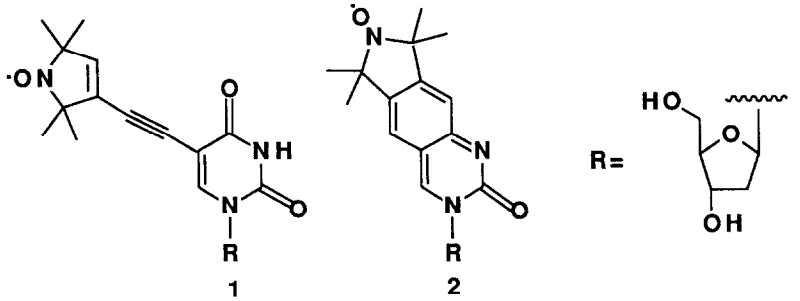
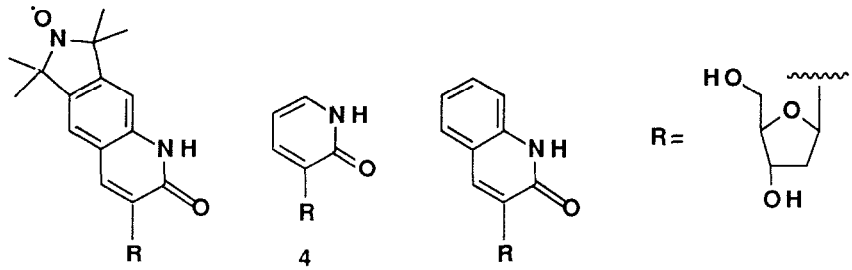
Abstract: 2'-Deoxy-C-ribosides **4** and **5** were prepared in optically active form by a route expected to be generally useful for the synthesis of the α- or β-anomers of 2'-deoxy-C-ribosides. Key steps are the addition of an organometallic reagent to aldehyde **7**, mesylation of the resulting alcohol, and stereospecific deprotection/cyclization to yield the 2'-deoxy-C-riboside (**7** + **8** → **9**/**10**; **9** → **11**).

Current interest in the synthesis of C-nucleosides stems primarily from the potential utility of these substances as antiviral and antitumor agents.[1] C-Nucleosides are also attractive as tools for the study of nucleic acids. We report herein a practical, stereocontrolled synthesis of 2'-deoxy-C-ribosides. Because what ultimately becomes the glycosidic bond is formed by addition of an organolithium reagent to the C-1 aldehyde of a hydroxyl-protected 2-deoxyribose, the synthesis offers considerable flexibility as to the nature of the C-1 substituent ("base"). Furthermore, either α- or β-anomers can be stereoselectively prepared.

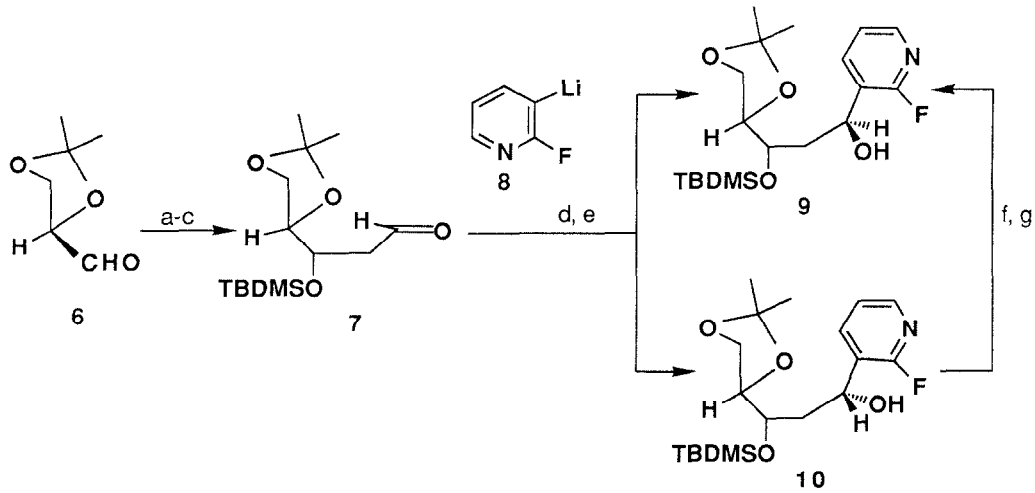
Our interest in C-nucleosides stems from their use as a substructure of nitroxide spin probes for nucleic acid dynamics. Ideally, in these molecules, relative motion of the nitroxide function and macromolecule is prohibited without incorporating structural features which disrupt the conformation, and hence dynamics, of the macromolecule. Spin probe **1** has been useful in this regard.[2] Although minimally disruptive of structure, in-depth studies reveal a residual motion of the nitroxide functionality relative to the DNA, likely due to limited rotation about the acetylene axis.[3] Inspection of CPK models suggested an alternative probe, **2**, in which this motion might be eliminated by fusion of the nitroxide-containing ring to the



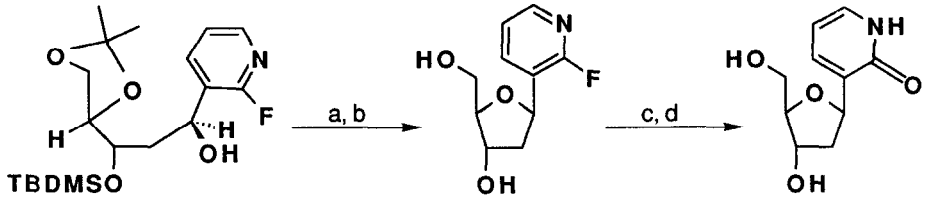
pyrimidine. Models suggested that in order to eliminate steric clash of the unnatural structural elements of **2** with the sugar-phosphate backbone, fusion as shown across pyrimidine carbons 4 and 5 (rather than 5 and 6) and incorporation of the central benzene ring might be critical. Unfortunately, precedent suggests that the π-system of the deoxycytidine analog **2** will likely exhibit unacceptably high chemical reactivity.[4] The C-nucleoside **3** might surmount this last hurdle; it is anticipated that **3** will form a stable base pair in duplex DNA opposite the known deoxyriboside of 2-aminopurine.[5] Reported herein are syntheses of the simpler substances **4** and **5**, whose chemistry and base pairing properties were deemed prudent to understand prior to embarking on a synthesis of **3**.



The protected 2′-deoxyribose **7** was prepared from (R)-2,3-isopropylidene glyceraldehyde in 59% overall yield as shown below.[6] The 9:1 mixture of epimers resulting from the diallyl zinc reaction[7] was carried forward and separated by column chromatography of **7**. Aldehyde **7** was treated at -78° with 3-lithio-2-fluoropyridine (**8**), conveniently available by direct deprotonation of 2-fluoropyridine,[8] to afford a 1:1 mixture of epimeric alcohols **9** and **10** which was separated by column chromatography (silica gel).[9] Conversion of **10** to **9** using the Mitsunobu



a. $(CH_2{=}CHCH_2)_2Zn$ (95%); b. TBDMSOTf (80%); c. O_3, Ph_3P (77%); d. **8**; e. H_2O (84%); f. DEAD, Ph_3P, $PhCO_2H$ (80%); g. NH_3, MeOH (92%)

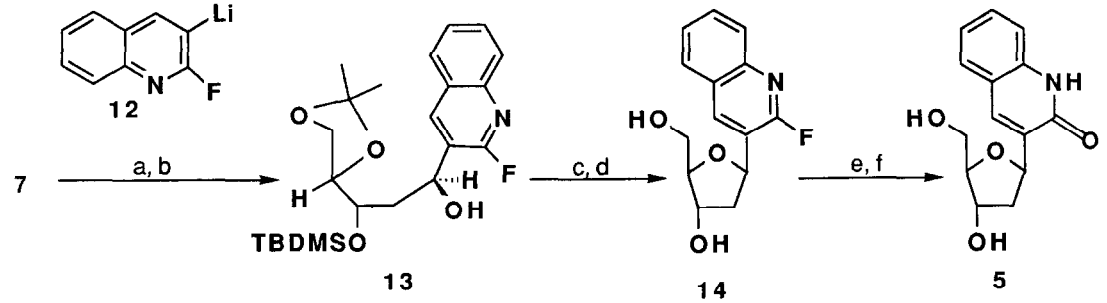


a. MsCl, Et_3N (99%); b. 4:1 TFA / $CHCl_3$ (75%); c. $C_6H_5CH_2OH$, KOH (83%); d. TMSI, CH_2Cl_2 (70%)

procedure[10] allowed both epimers to be used in further transformations. Mesylation of **9** now set the stage for the key cyclization reaction.[11,12] The selection of conditions for unmasking the 4'-hydroxyl function was found to be critical: excessively acidic media afforded a mixture of furanosides and pyranosides, each as a mixture of anomers. In contrast, treatment with 4:1 trifluoroacetic acid/chloroform[12] afforded exclusively **11**.[9] The stereospecificity of the cyclization could be demonstrated, analogous processing of **10** yielding the α-anomer of **11**. Finally, conversion of the fluoropyridine to the corresponding pyridone was accomplished by sequential displacement of fluoride with potassium benzyloxide, and removal of the benzyl group using trimethylsilyl iodide.

This route required only minor modification for the synthesis of **5**. Aldehyde **7** was treated with 3-lithio-2-fluoroquinoline (**12**),[8] available by direct deprotonation (LDA) of 2-fluoroquinoline, to afford **13**[9] and its epimer at the newly formed stereocenter as a separable (column chromatography, silica gel) 1:1 mixture. Deprotection/cyclization of the mesylate of **13** under conditions which were successful for the stereospecific conversion of **9** to **11** afforded in this case a mixture of the α- and β-anomers of **14**. Fortunately, this problem was alleviated by replacement of chloroform with methanol: exposure of the mesylate to 4:1 (v/v) trifluoroacetic acid/methanol for 15 minutes resulted in cyclization to **14** without anomerization in 70% isolated yield. Displacement of fluoride with sodium methoxide followed by deprotection with trimethylsilyl iodide afforded **5** in 76% yield for the two steps.

Efforts to incorporate **4** and **5** into DNA in order to examine their base pairing properties are underway and will be reported in due course.[13]



a. **12**; b. H_2O (60%); c. MsCl, Et_3N (90%); d. 4:1 TFA / MeOH (70%); e. MeONa, MeOH (93%); f. TMSI, CH_2Cl_2 (82%)

References and Endnotes

1. For reviews see: (a) Hacksell, U.; Daves, G.D., Jr. *Prog. Med. Chem.* **1985**, *22*, 1; (b) Suhadolnik, R.J. *Nucleoside Antibiotics* Wiley-Interscience: New York, 1970; (c) Buchanan, J.G. *Prog. Chem. Org. Nat. Prod.* **1983**, *44*, 243; (d) James, S.R. *J. Carb. Nucleosides Nucleotides* **1979**, *6*, 417.
2. (a) Spaltenstein, A.; Robinson, B.H.; Hopkins, P.B. *J. Am. Chem. Soc.* **1988**, *110*, 1299; (b) Spaltenstein, A.; Robinson, B.H.; Hopkins, P.B. *J. Am. Chem. Soc.* **1989**, *111*, 2303; (c) Spaltenstein, A.; Robinson, B.H.; Hopkins, P.B. *Biochemistry* **1989**, *28*, 9484.
3. Kirchner, J.J.; Hustedt, E.J.; Robinson, B.H.; Hopkins, P.B. *Tetrahedron Lett.* **1990**, *31*, 593.
4. Mruk, N.J.; Tieckelmann, H. *Tetrahedron Lett.* **1970**, 1209.
5. McLaughlin, L.W.; Leong, T.; Benseler, F.; Piel, N. *Nucleic Acids Res.* **1988**, *16*, 5631.
6. All substances were characterized by ^{1}H NMR; low or high resolution MS were obtained on key intermediates. Some key spectral data are as follows: **4**: ^{1}H NMR (200 MHz, D_2O): δ 1.88 (1H, ddd, H2' or 2", J=6, 10 and 13); 2.18 (1H, ddd, H2' or 2", J=2, 6 and 16); 3.56 (2H, m, H5', H5"); 3.90 (1H, m, H4'); 4.25 (1H, m, H3'); 5.07 (1H, dd, H1', J=6 and 10); 6.43 (1H, dd, H5, J=7); 7.33 (1H, dd, H6, J=2 and 7); 7.68 (1H, m, H4); LRMS (FABS, 3NBA): m/e 212 (M^++1), 176, 122.; HRMS (FABS, 3NBA): m/e calc'd 212.0904, found 212.0920; **5**: ^{1}H NMR (200 MHz, D_2O): δ 1.95 (1H, ddd, H2' or 2", J=6, 10 and 16); 2.39 (1H, ddd, H2' or 2", J=2, 6 and 16); 3.75 (2H, m, H5', H5"); 4.09 (1H, m, H4'); 4.40 (1H, m, H3'); 5.18 (1H, dd, H1', J=6 and 10); 7.18 (2H, m, H6, H7); 7.39 (2H, m, H5, H8); 7.89 (1H, m, H4); HRMS (FABS, 3NBA): m/e calc'd 262.1077, found 262.1050; **9**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.11 (3H, s, -CH_3); 0.12 (3H, s, CH_3); 0.87 (9H, s, -$C(CH_3)_3$); 1.35 (3H, s, -CH_3); 1.42 (3H, s, -CH_3); 1.86 (1H, ddd, CH_2, J=6, 10 and 16); 2.08 (1H, ddd, CH_2, J=3, 5 and 15); 3.80-4.21 (5H, m, -$CHCH_2O$, -CHOSi, -OH); 5.16 (1H, bd, -CHOH, J=10); 7.18 (1H, ddd, H5, J=2, 5, and 7); 7.94-8.10 (2H, m, H4, H6); LRMS (EI): m/e 284 (M^+-101), 270, 252, 198, 178, 126, 101; HRMS (FABS, 3NBA): m/e calc'd 386.2172, found 386.2159; **10**: ^{1}H NMR (200 MHz, $CDCl_3$): δ 0.05 (6H, s, 2x-CH_3); 0.86 (9H, s, $C(CH_3)_3$); 1.35 (3H, s, -CH_3); 1.41 (3H, s, -CH_3); 2.02 (2H, dd, CH_2, J=5 and 5); 3.06 (1H, d, -OH, J=4); 3.70-4.22 (4H, m, -$CHCH_2O$,-CHOSi); 5.21 (1H, m, -CHOH); 7.19 (1H, ddd, H5, J=2, 5, and 7); 7.93-8.09 (2H, m, H4, H6); LRMS (EI): m/e 284 (M^+-101), 270, 252, 198, 178, 126, 101; HRMS (FABS, 3NBA): m/e calc'd 386.2172, found 386.2159; **11** :^{1}H NMR (200 MHz, CD_3OD): δ 1.81 (1H, ddd, H2' or 2", J=6, 10, and 13); 2.25 (1H, m, H2' or 2"); 3.59 (2H, d, H5', H5", J=5); 3.89 (1H, m, H4'); 4.25 (1H, m, H3'); 5.22 (1H, dd, H1', J=6 and 10); 7.22 (1H, ddd, H5, J=2, 5, and 9); 8.00-8.12 (2H, m, H4, H6); LRMS (FABS, 3NBA): m/e 214 (M^++1), 194, 118; **13**:^{1}H NMR (200 MHz, $CDCl_3$) δ 0.13 (3H, s, -CH_3); 0.14 (3H, s, -CH_3); 0.89 (9H, s,-$C(CH_3)_3$); 1.39 (3H, s, -CH_3); 1.45 (3H, s,-CH_3); 1.90 (1H, ddd, -CH_2, J=6, 10, and 16); 2.22 (1H, m, CH_2); 3.81-4.18 (4H, m, -CH_2CH, -CHOSi); 4.41 (1H, d, -OH, J=2); 5.26 (1H, bd, -CHOH, J=10); 7.52 (1H, m, H6); 7.68 (1H, m, H7); 7.86 (2H, m, H5 , H8); 8.42 (1H, d, H4, J=10); HRMS (FABS, 3NBA): m/e calc'd 436.2316, found 436.2269; 14: ^{1}H NMR (200 MHz, CD_3OD): δ 1.87 (1H, ddd, H2' or 2", J=6, 10 and 16); 2.33 (1H, ddd, H2' or 2", J=2, 6 and 16); 3.63 (2H, m, H5', H5"); 3.93 (1H, m, H4'); 4.26 (1H, m, H3'); 5.30 (1H, dd, H1', J=5 and 10); 7.48 (1H, dd, H6 or H7, J=7); 7.64 (1H, dd, H6 or H7, J=2 and 7); 7.74 (1H, d, H5 or H8, J=8); 7.86 (1H, d, H5 or H8 , J=8); 8.52 (1H, d, H4, J=10); LRMS (FABS, 3NBA): m/e (M^++1) 264, 109.
7. (a) Brown, D.S.; Ley, S.V. *Tetrahedron Lett.* **1988**, *29*, 4869; (b) Mulzer, J.; Angermann, A. *Tetrahedron Lett.* **1983**, *24*, 2843; (c) Nagaoka, H.; Kishi, Y. *Tetrahedron* **1981**, *37*, 3873.
8. (a) Gribble, G.W.; Saulnier, M.G. *Tetrahedron Lett.* **1980**, *21*, 4137; (b) Marsais, F.; Bouley E.; Queguiner, G. *J. Organomet. Chem.* **1979**, *171*, 273.
9. For **9**, **10** and **13**, the depicted stereochemistry follows from Walden inversion during cyclization and stereochemical assignment of the anomeric centers of **4** and **5** by ^{1}H NMR. (NOE and coupling constants). For **4** an NOE is seen between H1' and H4', as well as between H4 and H5'/H5".
10. Mitsunobu, O. *Synthesis* **1981**, 1.
11. Belmans, M.; Vrijens I.; Esmans, E.L.; Lepoivre, J.A.; Alderweireldt, F.C.; Wotring, L.L.; Townsend, L.B. *Nucleosides Nucleotides* **1987**, *6*, 245.
12. Pankiewicz, K.W.; Sochacka, E.; Kabat, M.M.; Ciszewski, L.A.; Watanabe, K.A. *J. Org. Chem* **1988**, *53*, 3473.

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