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Towards 2',3'-Dideoxynucleoside Libraries: Synthesis of 3'-Alkylthio Analogues From An α,β-Unsaturated Aldehyde

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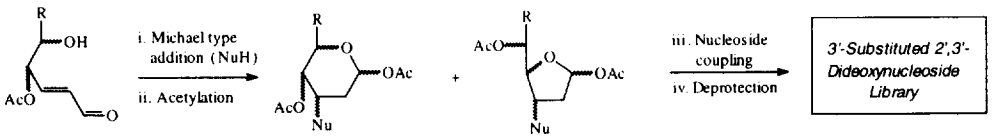
Abstract: Michael-type addition of alkanethiols to an α,β-unsaturated hexose aldehyde followed by acetylation, nucleoside coupling and deprotection afforded seventeen novel 3'-alkylthio-2',3'-dideoxynucleosides in three different sub-libraries. Copyright © 1996 Elsevier Science Ltd

The discovery of 2',3'-dideoxynucleosides like AZT (3'-azido-3'-deoxythymidine) and ddC (2',3'-dideoxycytidine) as anti-HIV agents[3,4] has recently stimulated much interest in nucleoside analogues as potential chemotherapeutic agents. Consequently, a large number of novel 2',3'-dideoxynucleoside analogues have been synthesised[5] and evaluated for *e.g.* anti-HIV activity. However, despite the many thousands novel compounds prepared and tested, the breakthrough in anti-HIV therapy has still to come, and AZT with its many serious side effects remains in clinical use.

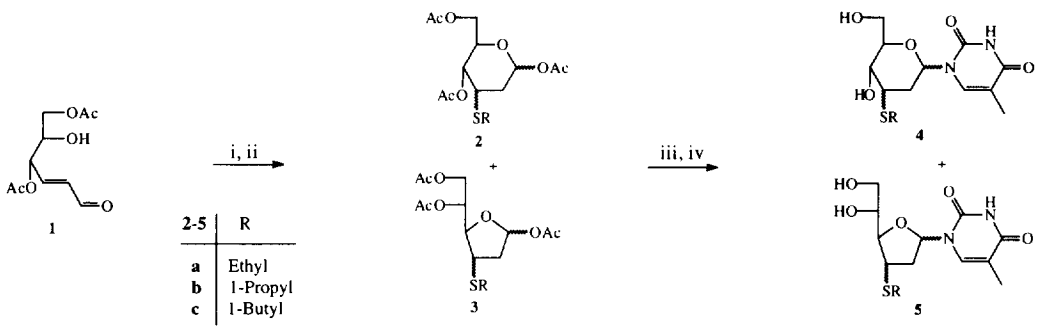
Combinatorial chemistry has emerged as a way of rapidly synthesising a large number of related molecules, either as individual compounds or as compound mixtures. This concept is now used extensively in drug discovery,[6,7] and development of efficient combinatorial methods for synthesis of molecular libraries of 2',3'-dideoxynucleoside analogues is an attractive target. In nucleoside chemistry, many efforts have been spent on isolating individual diastereomeric products. This can be considered unimportant when aiming at rapid screening and drug discovery, especially as the probability of finding interesting biological activity has proven rather limited. Earlier, we have developed a convergent method for synthesis of 3'-substituted 2',3'-dideoxynucleosides based on Michael type addition of different nucleophiles to α,β-unsaturated carbohydrate aldehydes[8-13] leading to diastereomeric products after troublesome chromatographic separations. Based on these results we propose a general scheme for combinatorial synthesis of libraries of 3'-substituted 2',3'-dideoxynucleosides as outlined in Figure 1. As an example, reaction of five different α,β-unsaturated carbohydrate aldehydes with five different nucleophiles followed by nucleoside coupling with five different nucleobases should afford 125 different compounds. However, if the formation of two 3-epimeric furanoses and two 3'-epimeric pyranoses, affording four carbohydrate intermediates, and the formation of two anomeric nucleosides for each intermediate is inherent in the chemistry of this strategy, a significant increase in the diversity of the library should result leading to the formation of a library (or a number of sub-libraries) containing up to 1000 compounds. This strategy bears conceptual similarities with the recently published reports on syntheses towards carbohydrate combinatorial libraries based on multicomponent reactions on glucals[14] or random galactosylation of unprotected *N*-acetylglucosamine.[15]



An example: 5 aldehydes x 5 nucleophiles x 5 nucleobases x 8 stereoisomers = *1000 member-library possible*

Figure 1

As the first step for evaluation of this strategy we here describe model results on addition of ethanethiol, 1-propanethiol and 1-butanethiol to the α,β-unsaturated hexose aldehyde **1**[16] followed by conversion of the resulting adducts into thymine nucleoside derivatives (Scheme 1).[17,18] Michael type addition of ethanethiol followed by acetylation and flash chromatography on a short silica gel column afforded in 74% yield a mixture of three 2,3-dideoxy-3-ethylthio pyranoses **2a** and two 2,3-dideoxy-3-ethylthio furanoses **3a** (**2a**:**3a** ~ 5:1 according to ^{1}H NMR and ^{13}C NMR). The formation of products with furanose configuration implies a 4-*O* to 5-*O* acetyl migration before acetylation of the anomeric position as observed before using other nucleophiles.[13] Addition of ethanethiol to aldehyde **1** employing slightly different reaction conditions has earlier been reported[9] to give exclusively pyranose products isolated in 82% yield without acylation. Following the same procedure as for **2a**/**3a**, addition of 1-propanethiol and 1-butanethiol and subsequent acetylation afforded a mixture of three pyranoses **2b** plus two furanoses **3b** (80% yield, **2b**:**3b** ~ 2:1) and a mixture of three pyranoses **2c** plus four furanoses **3c** (86% yield, **2c**:**3c** ~ 3:4), respectively.[17] From these experiments it seems that the longer the alkyl chain the more furanose product is being formed. Conversion of each of the three mixtures **2**/**3** into 3'-alkylthio-2',3'-dideoxynucleoside derivatives was achieved using standard conditions.[18-21] After deprotection and flash chromatography on a short silica gel column, a mixture of three pyranose nucleosides **4a** and two furanose nucleosides **5a** (88% yield, **4a**:**5a** ~ 5:1), a mixture of three pyranose nucleosides **4b** and two furanose nucleosides **5b** (89% yield, **4b**:**5b** ~ 5:2) and a mixture of four pyranose nucleosides **4c** and three furanose nucleosides **5c** (90% yield, **4c**:**5c** ~ 1:1) were obtained.



Scheme 1

i) RSH, DBU, THF; ii) Ac_2O, pyridine, DMAP, CH_2Cl_2; iii) silylated thymine, TMS-triflate, CH_3CN; iv) CH_3NH_2 in ethanol

Using this strategy, three small sub-libraries of five, five and seven nucleosides have been synthesised. Whereas it is straightforward on the basis of ^{13}C NMR data[17,18] to assign pyranose and furanose configuration to the individual compounds in the mixtures **2/3** and **4/5**, it is impossible to assign unambiguous configurations at C-3 and C-1. However, if all eight or most of the possible stereoisomers are present (as in mixtures **2c/3c** and **4c/5c**), or if the formation of biologically active compounds is the main target, this is not a crucial problem. The yields obtained are satisfactory (65-77% overall yields from **1** to mixtures **4/5**) and only short column chromatography (~"filtration") is needed. Seventeen novel 3'-alkylthio-2',3'-dideoxynucleosides have been prepared, all being present in sufficient quantity in the sub-libraries **4/5** to allow for biological evaluation which is presently in progress. Identification of active compounds in sub-libraries like **4/5** requires application of stereoselective synthetic routes and biological evaluation of the individual compounds. If larger libraries are synthesised, *e.g.* as suggested in Figure 1, deconvolution techniques are needed to identify active components. We are currently further evaluating both solution phase synthesis and solid phase synthesis of 2',3'-dideoxynucleoside libraries from α,β-unsaturated carbohydrate aldehydes.

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References and Notes

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17. *General method for synthesis of mixtures of hexoses 2 and 3:*
    To a solution of the α,β-unsaturated hexose aldehyde **1**[16] (6.35 g, 0.028 mol) in anhydrous THF (60 mL) at 0 °C under argon was added dropwise during 40 min a solution of the appropriate alkanethiol (0.028 mol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 4.26 g, 0.028 mol) in anhydrous THF (50 mL). After stirring for 20 min at 0 °C, analytical TLC (3% CH_3OH in CH_2Cl_2, v/v) indicated complete reaction and the solvent was removed under reduced pressure to give a yellow oil which was dissolved in anhydrous CH_2Cl_2 (75 mL). After addition of anhydrous pyridine (4.43 g, 0.056 mol), acetic anhydride (8.47 g,

0.083 mol) and 4-dimethylaminopyridine (DMAP, 0.023 g, 19 mmol) and stirring at rt for 3 h, the mixture was evaporated to dryness under reduced pressure to give an oil which was purified by silica gel column chromatography (75% CH_2Cl_2 in petroleum ether, v/v) to give a mixture of compounds **2** and **3**.

*Mixture of isomers of 2,3-dideoxy-3-ethylthio-1,5,6-tri-*O*-acetyl-D-hexopyranoses* ***2a*** *and 2,3-dideoxy-3-ethylthio-1,5,6-tri-*O*-acetyl-D-hexofuranoses* ***3a****:* Yield 6.80 g (74%). ^{13}C NMR ($CDCl_3$, selected signals): δ 98.06, 97.92 (C-1', **3a**); 92.51, 90.86, 90.68 (C-1', **2a**); 84.25, 84.15, (C-4', **3a**). MS (FAB/NBA): *m/z* 357 $(M+Na)^+$. Microanalysis for $C_{14}H_{22}O_7S,0.5H_2O$: Calcd. C 48.97, H 6.75; Found C 49.16, H 6.48.

*Mixture of isomers of 2,3-dideoxy-3-(1-propylthio)-1,5,6-tri-*O*-acetyl-D-hexopyranoses* ***2b*** *and 2,3-dideoxy-3-(1-propylthio)-1,5,6-tri-*O*-acetyl-D-hexofuranoses* ***3b****:* Yield 7.66 g (80%). ^{13}C NMR ($CDCl_3$, selected signals): δ 98.07, 97.94 (C-1', **3b**); 92.52, 90.88, 90.70 (C-1', **2b**); 84.20, 84.12, (C-4', **3b**). MS (FAB/NBA): *m/z* 371 $(M+Na)^+$. Microanalysis for $C_{15}H_{24}O_7S$: Calcd. C 51.71, H 6.94; Found C 51.75, H 6.98.

*Mixture of isomers of 3-(1-butylthio)-2,3-dideoxy-1,5,6-tri-*O*-acetyl-D-hexopyranoses* ***2c*** *and 3-(1-butylthio)-2,3-dideoxy-1,5,6-tri-*O*-acetyl-D-hexofuranoses* ***3c****:* Yield 8.56 g (86%). ^{13}C NMR ($CDCl_3$, selected signals) δ 98.07, 97.94, 97.45, 97.01 (C-1', **3c**); 92.52, 90.88, 90.71 (C-1', **2c**); 84.20, 84.14, 79.71, 79.41 (C-4', **3c**). MS (FAB/NBA): *m/z* 385 $(M+Na)^+$. Microanalysis for $C_{16}H_{26}O_7S$: Calcd. C 53.02, H 7.24; Found C 53.30, H 7.25.

18. *General method for synthesis of mixtures of nucleosides* ***4*** *and* ***5****:*

To a solution of the appropriate mixture of **2** and **3** (0.010 mol) and silylated thymine[19] (4.06 g, 0.015 mol) in anhydrous acetonitrile (50 mL) at 0 °C was added TMS-triflate (3.55 g, 0.016 mol) dropwise during 15 min. After stirring at rt for 6 h, analytical TLC (5% CH_3OH in CH_2Cl_2, v/v) indicated complete reaction, and the reaction mixture was diluted with CH_2Cl_2 (60 mL) and washed successively with a saturated aqueous solution of $NaHCO_3$ (3 x 30 mL) and H_2O (40 mL). The organic phase was dried (Na_2SO_4) and evaporated to dryness under reduced pressure to give an oil. To this residue was added a 33% solution of methylamine in absolute ethanol (100 mL) and the mixture was stirred at rt for 2 h until analytical TLC (7% CH_3OH in CH_2Cl_2, v/v) indicated complete reaction. The mixture was evaporated to dryness under reduced pressure and the residue was subjected to column chromatography on silica gel (3% CH_3OH in CH_2Cl_2, v/v) to give a mixture of compounds **4** and **5**.

Mixtures of isomers of 1-(2,3-dideoxy-3-ethylthio-D-hexopyranosyl)thymine ***4a*** *and 1-(2,3-dideoxy-3-ethylthio-D-hexofuranosyl)thymine* ***5a****:* Yield 2.78 g (88%). ^{13}C NMR (CD_3OD, selected signals): δ 88.99, 88.31, 87.26, 86.44 (C-1', C-4', **5a**); 83.50, 83.10, 82.34, 80.52, 79.93, 78.43 (C-1', C-4', **4a**). MS (FAB/NBA): *m/z* 317 $(M+H)^+$. Microanalysis for $C_{13}H_{20}N_2O_5S,1.0H_2O$: Calcd. C 46.69, H 6.63, N 8.38; Found C 46.80, H 6.19, N 8.42.

Mixtures of isomers of 1-(2,3-dideoxy-3-(1-propylthio)-D-hexopyranosyl)thymine ***4b*** *and 1-(2,3-dideoxy-3-(1-propylthio)-D-hexofuranosyl)thymine* ***5b****:* Yield 2.98 g (89%). ^{13}C NMR (CD_3OD, selected signals): δ 89.09, 88.35, 87.33, 86.43 (C-1', C-4', **5b**); 83.48, 83.07, 82.34, 80.56, 79.89, 78.44 (C-1', C-4', **4b**). MS (FAB/NBA): *m/z* 331 $(M+H)^+$. Microanalysis for $C_{13}H_{20}N_2O_5S,0.25H_2O$: Calcd. C 50.21, H 6.77, N 8.36; Found C 50.08, H 6.82, N 8.55.

Mixtures of isomers of 1-(3-(1-butylthio)-2,3-dideoxy-D-hexopyranosyl)thymine ***4c*** *and 1-(3-(1-butylthio)-2,3-dideoxy-D-hexofuranosyl)thymine* ***5c****:* Yield 3.10 g (90%). ^{13}C NMR (CD_3OD, selected signals): δ 89.18, 88.41, 87.85, 87.40, 86.48, 86.14 (C-1', C-4', **5c**); 83.79, 83.74, 83.57, 83.10, 82.41, 80.62, 79.96, 78.51 (C-1', C-4', **4c**). MS (FAB/NBA): *m/z* 345 $(M+H)^+$.

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