A SIMPLE TECHNIQUE TO DISTINGUISH BETWEEN C_S AND C_2 DIASTEREOMERIC DIOLS DERIVED FROM CHIRAL SUBSTRATES[1]

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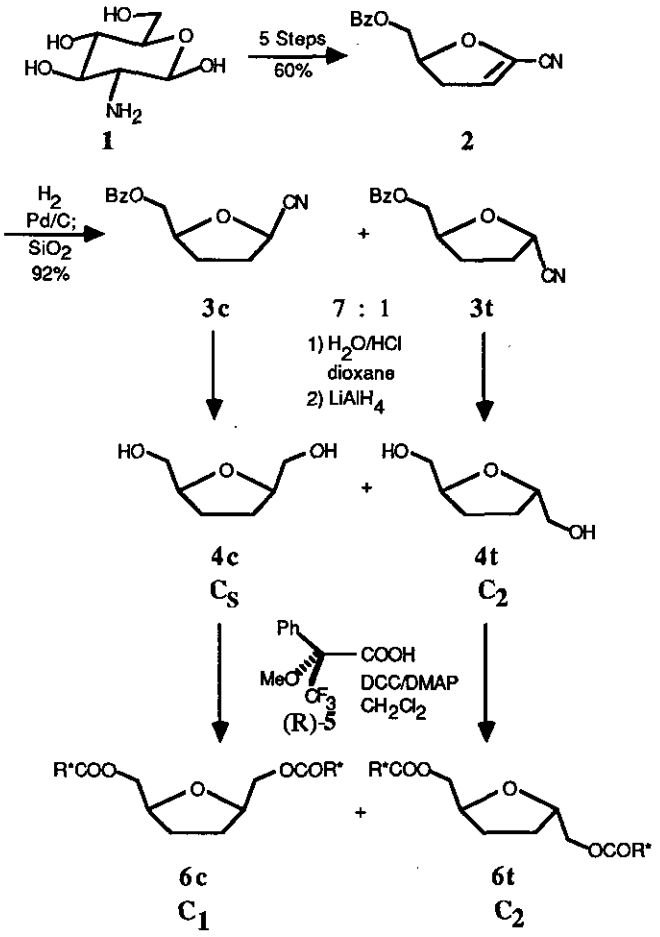
Abstract - A new technique which allows one to easily distinguish between a pair of C_S and C_2 diastereomeric diols derived from chiral material is described. The method involves inspection of the ^{13}C nmr spectra of the easily prepared Mosher's ester of each diol which permits the assignment to be made by simply counting the number of resonances observed.

Herein we report an easy technique to unequivocally assign the correct structures to a pair of diastereomeric diols derived from chiral material, one of which has C_S symmetry, the other C_2 symmetry. The method involves inspection of the ^{13}C nmr spectra of an easily prepared derivative of each diol which permits the assignment to be made by simply counting the number of resonances observed.

In the course of our work on the synthesis of potentially antiviral and/or antitumor modified C- and N-nucleosides from inexpensive precursors,[5] we prepared an easily separable 7:1 mixture of diastereomeric cyanobenzoates (**3c**) and (**3t**) in 92% yield by catalytic hydrogenation of the olefinic nitrile(**2**) (itself prepared in 5 steps and excellent overall yield from D-glucosamine (**1**)).[6] Unfortunately, the ^1H nmr spectra of these 2,3-dideoxyhexononitriles, unlike those of the corresponding 2-deoxy-3α-benzoyloxy analogues,[5a] do not allow a simple assignment of the stereochemistry since the coupling pattern for the low field proton α to the cyano group is very complex in each. Therefore we sought a simple and sure method for the structural assignment. Acidic hydrolysis of the nitrile group of **3c** and **3t** gave the corresponding acids which were reduced with $LiAlH_4$ to generate the diastereomeric diols *cis* (*S,R*)- and *trans* (*S,S*)-tetrahydrofuran-2,5-dimethanols (**4c** and **4t**). Both of these diols have symmetry properties (either a symmetry plane or a C_2 axis) which reduce the number of proton and carbon signals by half,

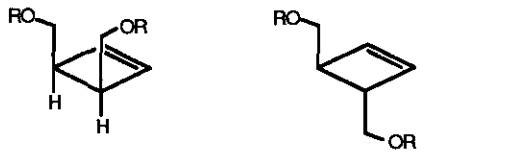
but because there is no magnetically active nuclei in the symmetry plane, simple ^{1}H or ^{13}C nmr does not allow one to distinguish between them. Although these diols could potentially be distinguished by optical rotation - since **4c** is C_S, its rotation should be zero, while the C_2 isomer (**4t**) should have some rotation - the small amount of **4t** made this technique somewhat questionable.[7] Therefore we developed the following simple alternative. Treatment of **4c** and **4t** separately with (*R*)-(+)-Mosher's acid ((*R*)-**5**) and dicyclohexylcarbodiimide (DCC) in the presence of 4-dimethylaminopyridine (DMAP) afforded in excellent yield the corresponding cis and trans diesters



(**6c**) and (**6t**). In the former isomer (**6c**) the plane of symmetry present in **4c** is no longer maintained and the symmetry is now C_1, whereas in the trans isomer (**6t**), the C_2 axis of symmetry is still present. Therefore simple

inspection of the ^{13}C nmr spectra of **6c** and **6t** permitted the assignment of structure: compound (**6t**) showed only 3 absorptions for the six sugar carbons (and no doubling of peaks for the ester groups) while **6c** showed a doubling of each of the upfield carbons of the sugar rings, i.e., all 6 carbons are different.[8,9] Thus the structures of the cyanosugars (**3c**) and (**3t**) could be assigned with confidence.

We have examined one other example to show the generality of this technique. The two diastereomeric diols, *cis* (1*R*,2*S*)- and *trans* (1*S*,2*S*) 3-cyclobutene-1,2-dimethanol (**7c**) and (**7t**) were prepared.[10] Again the simple ^{1}H and ^{13}C nmr did not allow structural assignment of the C_S and C_2 isomers. Therefore, the bis-Mosher's ester derivatives (**8c**) and (**8t**) were prepared by the method described above. Their ^{13}C nmr spectra again showed the expected results, the C_S diol (**7c**) gave the C_1 diester (**8c**) (with a doubling of most of the peaks in the nmr) while the C_2 diol (**7t**) gave the C_2 diester (**8t**) (and no doubling of the nmr absorptions).



C_S 7c R = H **7t** R = H **C_2**

C_1 8c R = (R)-COCPh(MeO)(CF_3) **8t** R = (R)-COCPh(MeO)(CF_3) **C_2**

An advantage of this method over the alternative of optical rotation is that it can be used even when the C_S isomer is not completely pure since small amounts of impurities (even chiral impurities) do not affect the doubling of the major peaks in the ^{13}C nmr. It is important to point out that this technique is not applicable if the C_2 isomer is available only in racemic form, since then diastereomers would result from the derivatization and a doubling of peaks would be observed. Finally the method can also be used when the C_2 isomer is not completely optically pure since a small amount of racemic material is easily discerned in the ^{13}C nmr. Thus we have developed a simple derivatization - ^{13}C nmr technique for distinguishing between C_S and C_2 diastereomeric pairs of diols prepared from chiral materials.

EXPERIMENTAL

^{1}H Nmr were recorded on a Bruker AM-360 spectrometer, operating at 360.134 MHz. ^{13}C Nmr spectra were recorded on the AM-360, operating at 90.556 MHz. Infrared spectra were recorded on a Perkin-Elmer series 1600 FTIR spectrometer as a liquid film (neat). All the high resolution mass spectra were recorded on a ZAB 7070 HP spectrometer at the University of California, Riverside, CA. The samples were analyzed by desorptive chemical ionization (DCI) using ammonia and therefore the molecular ions are all represented as M+1 or M+NH_4. ^{1}H Nmr and ^{13}C nmr data are reported in parts per million (δ) downfield from tetramethylsilane. The following abbreviations are used: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, app = apparent. Second order spectra in which couplings cannot be obtained by inspection are reported as multiplets and the line spacings are given in Hertz (Hz). Ir data are reported in wave numbers (cm^{-1}). Thin layer chromatography (tlc) was performed using Merck silica gel 60 F_{254} 0.2 mm plates. All inorganic solutions are aqueous and concentrations are indicated in percent weight, except brine (saturated sodium chloride). The following solvents and reagents were distilled from the indicated agent under dry nitrogen: tetrahydrofuran (THF) from sodium benzophenone ketyl and dichloromethane from calcium hydride. Other solvents were used without purification. All other reagents were purified by literature procedures.

α and β 2,5-Anhydro-6-*O*-benzoyl-3,4-dideoxygluconononitriles, 3t and 3c. A mixture of **2** and the corresponding α and β 3,4-didehydro-3,4-dideoxy isomers (in an approximately 8:2:1 ratio), prepared by reduction[6] of 2,5-anhydro-4, 6-di-*O*-benzoyl-2,3-didehydro-3-deoxygluconononitrile (366 mg, 1 mmol), was dissolved in methanol (50 ml) and the solution was saturated with hydrogen. Palladium on carbon (10%, 200 mg) was then added, and hydrogen was bubbled through the solution for 1 h. After filtering through Celite, the methanol was removed under reduced pressure, and the residue was subjected to flash chromatography on silica gel (hexane/ethyl acetate = 5/1). The anomers of 2,5-anhydro-6-*O*-benzoyl-3,4-dideoxygluconononitrile were isolated as colorless oils (340 mg, 92%): **3t** and **3c**, in a ratio of 1:7.

3t: $[\alpha]_D^{25}$ = +12° (c, 2.5 in $CHCl_3$). ^{1}H Nmr ($CDCl_3$) δ: 8.03-8.00 (2H, m), 7.56 (1H, bt, J = 7.3 Hz), 7.43 (2H, t, J = 7.56 Hz), 4.82 (1H, dd, J = 7.2, 3.6 Hz), 4.53 (1H, m), 4.40 (1H, dd, J = 11.9, 3.6 Hz), 4.30 (1H, dd, J = 11.9, 5.7 Hz), 2.29 (3H, m), 1.91 (1H, m). ^{13}C Nmr ($CDCl_3$) δ: 165.98, 132.99, 129.40, 129.33,

128.14, 118.75, 77.76, 66.58, 65.33, 31.02, 26.64. Ir (neat): 2944, 1715, 1595, 1577, 1445, 1308, 1268, 1170, 1113, 1073, 1021, 711 cm^{-1}. HRms (*m/z*): 232.0974, calcd for $C_{13}H_{14}O_3N$ 232.0974.

3c: $[\alpha]_D^{25}$ = -1.2° (c, 4.1 in $CHCl_3$). ^1H Nmr ($CDCl_3$) δ: 8.06-8.04 (2H, m), 7.50 (1H, bt, *J* = 7.5 Hz), 7.38 (2H, t, *J* = 7.6 Hz), 4.68 (1H, dd, *J* = 7.4, 3.6 Hz), 4.44-4.30 (3H, m), 2.35-1.95 (4H, m). ^{13}C Nmr ($CDCl_3$) δ: 165.78, 132.69, 129.21, 129.16, 127.91, 118. 95, 78.61, 66.09, 65.17, 31.38, 26.78. Ir (neat): 2944, 1715, 1595, 1577, 1445, 1308, 1268, 1170, 1113, 1073, 1021, 712 cm^{-1}. HRms (*m/z*): 232.0974, calcd for $C_{13}H_{14}O_3N$ 232.0974.

β-2,5-Anhydro-6-*O*-benzoyl-3,4-dideoxygluconic acid. To a 1.5 M solution of dry HCl gas in dioxane (14 ml) were added compound (**3c**) (2.31 g, 10 mmol) and water (540 mg, 30 mmol), and the mixture was heated in a pressure bottle for 12 h at 60 °C. Ether (50 ml) was added, the precipitate of ammonium chloride was filtered off, and the filtrate was evaporated under reduced pressure. The crude acid was first purified by flash chromatography on silica gel (ethyl acetate/methanol/acetone/ water = 10/1/1/1) and then by ion exchange chromatography (Dowex 50, H^+ form, eluent 1M HCl in 2-propanol) to yield pure β-2,5-anhydro-6-*O*-benzoyl-3,4-dideoxygluconic acid (2.08 g, 83%) as a colorless oil: $[\alpha]_D^{25}$ = +33.6° (c, 1.4 in $CHCl_3$). ^1H Nmr ($CDCl_3$) δ: 9.89 (1H, bs), 8.06-8.03 (2H, m), 7.54 (1H, tt, *J* = 7.3, 1.3 Hz), 7.41 (2H, bt, *J* = 7.7 Hz), 4.66 (1H, dd, *J* = 12.0, 6.3 Hz), 4.58 (1H, dd, *J* = 8.2, 5.6 Hz), 4.52-4.43 (1H, m), 4.40 (1H, dd, *J* = 12, 2.8 Hz), 2.39-2.21 (2H, m), 2.13-2.05 (1H, m), 1.86-1.77 (1H, m). ^{13}C Nmr ($CDCl_3$) δ: 176.18, 166.79, 133.16, 129.63, 129.49, 128.31, 79.35, 77.21, 66.21, 30.24, 27.08. Ir (neat): 3560-2341, 1750, 1715, 1601, 1580, 1448, 1350, 1315, 1273, 1176, 1092, 1024, 714 cm^{-1}. HRms (*m/z*): 251.0919, calcd for $C_{13}H_{15}O_5$ 251.0919.

(*S,R*)-Tetrahydrofuran-2,5-dimethanol, 4c. To a solution of the β-dideoxy acid (279 mg, 1.12 mmol) in dry THF (20 ml) was added lithium aluminum hydride (213 mg, 5.6 mmol) and the mixture was refluxed overnight. Usual workup was followed by addition of silica gel (2 g) and evaporation of the solvents *in vacuo*. Flash chromatography on silica gel (chloroform/methanol = 9/1) gave the cis diol (**4c**) (100 mg, 76%) as an oil. ^1H Nmr ($CDCl_3$) δ: 4.27 (2H, bs), 4.00-3.96 (2H, m), 3.64 (2H, dd, *J* = 11.8, 2.8 Hz), 3.40 (2H, dd, *J* = 11.8, 5.4 Hz), 1.84-1.78 (2H, m), 1.74-1.68 (2H, m). ^{13}C Nmr ($CDCl_3$) δ: 80.12, 64.48, 26.89. Ir (neat): 3635-3028 b, 2929, 2873, 1456, 1100, 1052, 880, 814 cm^{-1}.

(*S*,*S*)-Tetrahydrofuran-2,5-dimethanol, 4t. To a solution of the α-dideoxy acid (126 mg, 0.50 mmol), prepared from the nitrile (**3t**) by an analogous procedure to that described above for the β-isomer, in dry THF (15 ml) was added lithium aluminum hydride (95 mg, 2.5 mmol) and the mixture was refluxed overnight. Usual workup was followed by addition of silica gel (2 g) and evaporation of the solvents *in vacuo*. Flash chromatography on silica gel (chloroform/methanol = 9/1) gave the trans diol (**4t**) (54 mg, 82%) as an oil: $[\alpha]_D^{25}$ = +33° (c, 2.2 in $CDCl_3$). ^1H Nmr ($CDCl_3$) δ: 4.14-4.08 (2H, m), 3.63 (2H, dd, *J* = 11.8, 2.8 Hz), 3.48 (2H, dd, *J* = 11.8, 6.6 Hz), 3.29 (2H, bs), 1.99-1.91 (2H, m), 1.70-1.59 (2H, m). ^{13}C Nmr ($CDCl_3$) δ: 80.07, 64.79, 27.49. Ir (neat): 3674-3017 b, 2927, 2871, 1455, 1100, 1049, 893, 805 cm^{-1}.

(*S*,*R*)-Tetrahydrofuran-2,5-dimethanol, bis-Mosher's ester, 6c. A mixture of the cis diol (**4c**) (77 mg, 0.58 mmol), (*R*)-(+) Mosher's acid ((*R*)-**5**) (326 mg, 1.39 mmol), dicyclohexylcarbodiimide (DCC) (311 mg, 1.51 mmol) and 4-dimethylaminopyridine (DMAP) (184 mg, 1.51 mmol) in dry dichloromethane (7 ml) was refluxed for 48 h. The solids were filtered off, and the filtrate was subjected to flash chromatography on silica gel (hexane/ethyl acetate = 2/1). The cis diester (**6c**) was isolated (226 mg, 69%) as an oil. ^1H Nmr ($CDCl_3$) δ: 7.52-7.51 (4H, m), 7.40-7.37 (6H, m), 4.29-4.13 (6H, m), 3.53 (6H, s), 1.98-1.87 (2H, m), 1.67-1.52 (2H, m). ^{13}C Nmr ($CDCl_3$) δ: 166.40, 166.37 (2 C=O), 132.18, 132.13, 129.64, 129.62, 128.39, 127.28, 127.26 (7 of 8 aromatic C's), 128.04, 124.84, 121.64, 118.44 (CF_3 quartet), 86.80, 86.60, 86.40, 86.20 (C-CF_3 quartet), 76.74, 76.67 (2 CH_2O), 67.87, 67.66 (2 CHO), 55.44, 55.42 (2 OCH_3), 27.63, 27.49 (2 CH_2). Ir (neat): 2953, 1751, 1495, 1452, 1273, 1244, 1170, 1123, 1108, 1082, 1021, 1001, 766, 720, 698 cm^{-1}. HRms (*m/z*): 565.1661, calcd for $C_{26}H_{27}O_7F_6$ 565.1661.

(*S*,*S*)-Tetrahydrofuran-2,5-dimethanol, bis-Mosher's ester, 6t. A mixture of the trans diol (**4t**) (38 mg, 0.29 mmol), (*R*)-(+) Mosher's acid ((*R*)-**5**) (161 mg, 0.69 mmol), DCC (153 mg, 0.74 mmol) and DMAP (91 mg, 0.75 mmol) in dry dichloromethane (5 ml) was refluxed for 48 h. The solids were filtered off, and the filtrate was subjected to flash chromatography on silica gel (hexane/ethyl acetate = 2/1). The trans diester (**6t**) was isolated (124 mg, 77%) as an oil: $[\alpha]_D^{25}$ = +8° (c, 3.5 in $CDCl_3$). ^1H Nmr ($CDCl_3$) δ: 7.54-7.52 (4H, m), 7.40-7.35 (6H, m), 4.40-4.37 (6H, m), 3.53 (6H, s), 1.96-1.94 (2H, m), 1.66-1.60 (2H, m). ^{13}C Nmr (C_6D_6) δ: 167.01 (C=O), 133.34, 130.30, 129.13, 128.32 (4 aromatic C's), 129.46, 126.29, 123.11, 119.92 (CF_3 quartet), 85.93, 85.83, 85.73, 85.63 (C-CF_3 quartet), 76.96 (CH_2O), 67.81 (CHO), 55.81 (OCH_3), 28.13

(CH_2). Ir (neat): 2949, 2360, 2336, 1750, 1496, 1452, 1274, 1244, 1170, 1123, 1108, 1082, 1023, 1001, 766, 720, 698, 668 cm^{-1}.

(*S*,*S*)-3-Cyclobutene-1,2-dimethanol, bis-Mosher's ester, 8t. A mixture of (1S, 2S) 3-cyclobutene-1,2-dimethanol (**7t**)[10] (30 mg, 0.26 mmol), (*R*)-(+) Mosher's acid ((*R*)-**5**) (159 mg, 0.68 mmol), DCC (140 mg, 0.68 mmol) and DMAP in dry dichloromethane (5 ml) was refluxed for 20 h. The mixture was cooled to room temperature and poured into 20 ml of ether. The insoluble material was removed by filtration and the filtrate was washed with 1N HCl, saturated aqueous $NaHCO_3$, and brine. The organic phase was dried over $MgSO_4$ and evaporated *in vacuo*. The residue was purified by flash chromatography on silica gel (cyclohexane/ethyl acetate = 3/1). The trans diester (**8c**) was isolated as a colorless oil (106 mg, 75%). ^1H Nmr ($CDCl_3$) δ: 7.52-7.50 (4H, m), 7.41-7.37 (6H, m), 6.05 (2H, s), 4.36 (2H, dd, J = 11.1, 6.1 Hz), 4.29 (2H, dd, J = 11.1, 5.8 Hz), 3.53 (6H, s), 2.89-2.81 (2H, m). ^{13}C Nmr ($CDCl_3$) δ: 167.44 (C=O), 137.51 (C=C), 132.15, 129.66, 128.42, 127.26 (4 aromatic C's), 128.03, 124.85, 121.66, 118.47 (CF_3 quartet), 85.03, 84.72, 84.41, 84.10 (C-CF_3 quartet), 66.94 (CH_2O), 55.40 (m, OCH_3), 45.02 (CH).

(*S*,*R*)-3-Cyclobutene-1,2-dimethanol, bis-Mosher's ester, 8c. This bis ester was prepared from (S,R)-3-cyclobutene-1,2-dimethanol (**7c**)[10] by a route identical to that described for **8t** above. Yield 70%. ^1H Nmr ($CDCl_3$) δ: 7-51-7.48 (4H, m), 7.43-7.35 (6H, m), 6.03 (2H, s), 4.38-4.21 (4H, m), 3.52 (6H, s), 3.28-3.21 (2H, m). ^{13}C Nmr ($CDCl_3$) δ: 166.19 (2 C=O), 137.60, 137.49 (2 C=C), 132.07, 132.04 (2 aromatic quat. C's), 129.58, 128.36, 127.17 (m) (3 aromatic C's), 127.99, 124.80, 121.61, 118.42 (CF_3 quartet), 85.02, 84.97, 84.72, 84.67, 84.41, 84.34, 84.10, 84.05 (2 CF_3 quartets), 65.44, 65.40 (2 CH_2O), 55.33 (m, OCH_3), 43.92, 43.87 (2 CH).

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REFERENCES AND NOTES

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