Diastereoselective Synthesis of (2*R*,4*S*,5*S*)-(+)-5-(2,2-Dichloroacetamido)- 4-(4-nitrophenyl)-2-aryl-1,3-dioxanes

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(2*R*,4*S*,5*S*)-(+)-5-(2,2-Dichloroacetamido)-4-(4-nitrophenyl)-2-aryl-1,3-dioxanes **3-8** were synthesized with high diastereoselectivity and good yields. The structures of acetals were determined and the configurations were confirmed by 2D-NMR (NOESY) and X-ray crystallographic analysis.

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Introduction.

Acetals are important in synthetic pharmaceuticals [1] and phytopharmaceuticals [2] as intermediates or as final products. Protection of the carbonyl group of aldehydes or ketones can be accomplished by acetalization[3]. Asymmetric reductions of prochiral aromatic ketones in the presence of a hydroxymonosaccharide acetal have been described[4].

Acetals can be synthesized in a number of ways. The most common and general approach is the acid catalyzed reaction of alcohols with aldehydes or ketones under (continuous) azeotropic remove of water in a Dean-Stark trap [5], or by dehydrating agents [6]. Most chiral acetals can be synthesized from chiral substrate [7], diastereoselective addition [8] or catalyzed by chiral catalyst [9]. In the cases that the chiral 1,3-diol possesses a C_2 axis of symmetry, only one diasteromer is formed because transposition of the nonoxygen ligands at the acetal center leads to the same compound. If there is no C_2 axis, two diastereomers can be formed. In acetalization reactions with chiral diols without a C_2 symmetry axis, the formation of one diastereomer is often favoured over the formation of the other one [10]. (1*S*,2*S*)-(+)-2-Amino-1-(4-nitrophenyl)-1,3-propanediol **1** is a chiral 1,3-diol with chiral centers at the 1- and 2-positions and without a C_2 symmetry axis. We carried out the reaction of 1,3-diol **1** and aryl aldehydes under acidic conditions. Here, we reported the results of diastereoselective synthesis and structural determination.

(2*R*,4*S*,5*S*)-(+)-5-(2,2-dichloroacetamido)-4-(4-nitrophenyl)-2-aryl-1,3-dioxanes **3-8** were obtained (Scheme 1) from the reaction of substituted benzaldehydes and (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **1**, the enantiomer that is discarded during the commercial production process of chloramphenicol. Compound **1** is produced with high diastereoselectivity and in good yield. By this method, only the above specified enantiomers were obtained along with a only small amount of polymer. The absolute configuration of these products was determined using 2D-NMR and X-ray crystallographic analysis.

Results and Discussion.

By analysis of the space-filling model, we predicted that the conformations of the products would be (2*R*,4*S*,5*S*) (Figure 1). For the case of 5-(2,2-dichloroacetamido)-2-(3-nitrophenyl)-4-(4-nitrophenyl)-1,3-dioxane **6**, the structure has been confirmed by a NOESY experiment (Figure 2) [11]. The stereochemistry of 5-(2,2-dichloroacetamido)-2-(4-methyloxyphenyl)-4-(4-nitrophenyl)-1,3-dioxane **7** was established unequivocally by X-ray crystallographic analysis (Figure 3).

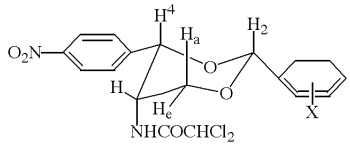
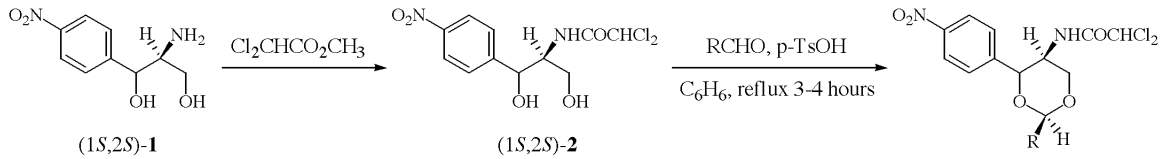


Figure 1. Predicted conformation for **3-8**.

The anticipated cross-peaks between H-2 and H-4 (shown in Figure 1) are readily identified. These peaks are denoted in the spectra with A and they clearly demonstrate the mutual diaxial relationship between H-2 and H-4. As to other probable conformational relationships between H-2 and H-4: (a) eq H-2- ax H-4, (b) ax H-2- eq H-4, (c) eq H-2- eq H-4, none of these cross-peaks are seen in the spectrum. Although the

Scheme 1



(1*S*,2*S*)-**1** (1*S*,2*S*)-**2** (2*R*,4*S*,5*S*)-**3-8**

R = C_6H_5 (**3**), O-HOC_6H_4 (**4**), O-ClC_6H_4 (**5**), *m*-$NO_2C_6H_4$ (**6**), *p*-$CH_3C_6H_4$ (**7**), 2-furyl (**8**).

Table I

Selected geometric parameters of **7** (bond lengths Å,)

Cl(1)-C(19)	1.765(4)	Cl(2)-C(19)	1.774(5)	O(1)-C(3)	1.437(4)
O(1)-C(4)	1.434(4)	O(2)-C(2)	1.436(4)	O(2)-C(3)	1.422(4)
O(5)-C(14)	1.373(5)	O(5)-C(17)	1.446(6)	O(6)-C(18)	1.220(4)
N(1)-C(8)	1.470(4)	N(2)-C(1)	1.465(4)	N(2)-C(18)	1.342(4)
C(1)-C(2)	1.530(5)	C(1)-C(4)	1.540(5)	C(3)-C(11)	1.488(5)
C(4)-C(5)	1.493(5)				

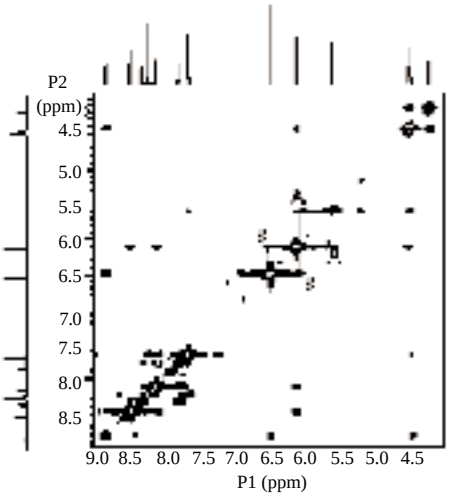


Figure 2. NOESY spectrum of **6**

absence of certain cross-peaks does not necessarily prove that no interaction exists, it is likely that they would have been if the mentioned conformational relationship (a) to (c). Space-filling models show that these three conformations between (a) and (c) are highly unlikely, as a consequence of large unavoidable steric hindrance by axial subsituents. According to the

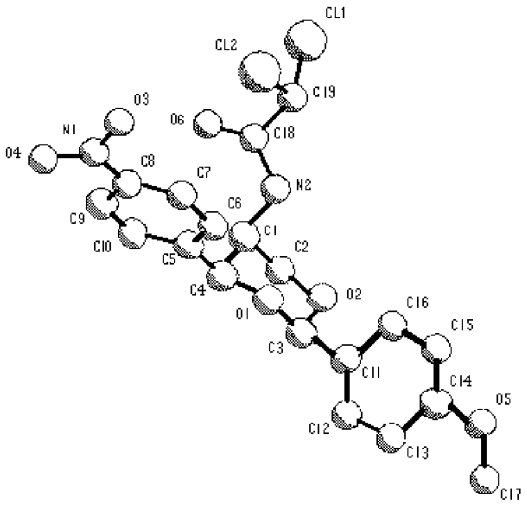


Figure 3. X-ray crystal structure of **7**.

Table II

Selected geometric parameters of **7** (bond angles, °)

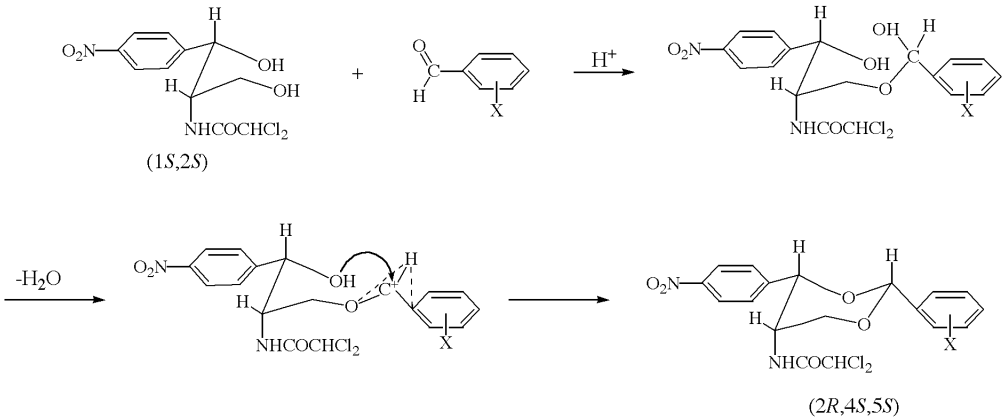
C(3)-O(1)-C(4)	111.3(2)	C(2)-O(2)-C(3)	112.4(3)
O(4)-N(1)-C(8)	117.5(3)	C(1)-N(2)-C(18)	121.8(3)
C(2)-C(1)-C(4)	108.0(3)	O(2)-C(2)-C(1)	110.0(3)
O(2)-C(3)-C(11)	108.9(3)	O(1)-C(4)-C(1)	108.2(3)
C(4)-C(5)-C(6)	121.6(3)	C(4)-C(5)-C(10)	119.4(3)
C(3)-C(11)-(12)	121.9(3)	C(3)-C(11)-C(16)	120.0(3)
O(6)-C(18)-N(2)	124.3(3)	O(6)-C(18)-C(19)	121.9(3)
Cl(1)-C(19)-(18)	109.9(3)	Cl(2)-C(19)-C(18)	108.9(3)
C(14)-O(5)-C(17)	117.4(4)	O(3)-N(1)-C(8)	118.7(3)
N(2)-C(1)-C(2)	110.0(3)	N(2)-C(1)-C(4)	1110(3)
O(1)-C(3)-O(2)	109.6(3)	O(1)-C(3)-C(11)	107.6(3)
O(1)-C(4)-C(5)	108.1(3)	C(1)-C(4)-C(5)	113.1(3)
N(1)-C(8)-C(7)	117.7(3)	N(1)-C(8)-C(9)	119.0(3)
O(5)-C(14)-C(13)	125.3(4)	O(5)-C(14)-C(15)	114.4(4)
N(2)-C(18)-C(19)	113.8(3)	Cl(1)-C(19)-Cl(2)	108.9(2)

conformational analysis of **6**, we consider that its absolute configuration is (2*R*,4*S*,5*S*). Because the ^{1}H and ^{13}C-NMR spectra of all the synthesized acetals resemble each other closely, we assume all these compounds have the same configuration as that described for **6**. The result of X-ray crystallographic analysis of **7** add more evidence for the configuration of these acetals.

5-(2,2-Dichloroacetamido)-2-(4-methyloxyphenyl)-4-(4-nitrophenyl)-1,3-dioxane **7**, $C_{19}H_{18}O_6N_2Cl_2$ (Mr = 441.26), crystallizes in the orthorhombic space group $P2_12_12_1$, with four molecules in a unit cell. Crystal data are a = 12.038(1), b = 12.855(1), c = 13.010(1) Å, v = 2013.3(3) $Å^3$, R_f = 0.043, R_w = 0.043, Z = 4, Dc = 1.456g/cm^3. The six-member ring is in chair form. The two large groups, *p*-nitrophenyl and *p*-methyloxyphenyl, are all equatorial to avoid steric hindrance, and the 2,2-dichloroacetamido group is axial. The dihedral angle between the two phenyl rings is 108.68° (13).

According to these results, a probable mechanism for the diastereoselective acetal formation is shown in Scheme 2. As the hemiacetal is formed, it combines with H^+; followed by elimination of water to form the carbocation. The hydroxyl in 1-position can attach the carbocation from the up face or the down face, and (2*S*,4*S*,5*S*)- or (2*R*,4*S*,5*S*)-acetal is formed respectively. However, the (2*R*,4*S*,5*S*)-acetal is thermodynamically more stable than that of the (2*S*,4*S*,5*S*)-acetal.

Scheme 2



EXPERIMENTAL

The (1*S*,2*S*)-(+)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **1** was obtained from the Wuhan Pharmacy Plant and purified by recrystallization in methanol. Melting points were measured in a XT-4 melting point measurement and are uncorrected. Column chromatography was carried out using silica gel. IR spectra were recorded on a 170 SX Nicolet FT-IR instrument and are given in cm^{-1}. ^1H and ^{13}C NMR were recorded on XL-200 spectrometer, chemical shifts were given in ppm (internal standard tetramethylsilane) and the NOESY spectrum was acquired on INOVA-500 spectrometer. Mass spectra were performed on a ZAB 3F-HF mass spectrometer. Optical rotation values were obtained using a WZZ-2A polarimeter. Elemental Analysis were determined by 240B Elemental Autoanalyzer. X-ray crystal data was collected by Nonius MAC DIP-2030K diffractometer.

(1*S*,2*S*)-2-dichloroacetamido-1-(4-nitrophenyl)-1,3-propanediol (**2**).

A mixture of 30 g (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)-1,3-propanediol **1**, 16.7 ml methyl dichloroacetate and 50 ml methanol was heated to 70 °C and kept for 2 hours, cooled to collect precipitate, followed by recrystallization of the reaction product **2** from methanol. Yield 44.7 g (97.8 %) of light yellow crystal. mp 149-150 °C, lit. [12] mp 150 °C.

General Procedure for the Preparation of (2*R*,4*S*,5*S*)-(+)-2-Aryl-5-(2,2-dichloroacetamido)-4-(4-nitrophenyl)-1,3-dioxanes 3-8.

This procedure is based on literature methods [13]. A mixture of **2** (3 g, 9.2 mmol), aryl aldehyde (19 mmol) and *p*-toluenesulfonic acid (0.06 g) in dry benzene (200 ml) was refluxed and the water removed by continuous azeotropic distillation (3 hours). The solvent was distillated under vacuum and the residue was taken up in ether. The ethereal extract was washed with cold sodium carbonate (Na_2CO_3) (50 ml, 5%) solution, water and saturated brine (2 × 50 ml) respectively, then dried with sodium sulfate (Na_2SO_4) over night. The solution was filtered and concentrated. The residue was recrystallized from benzene-petroleum ether (1:2) or purified by column-chromatogram.

(2*R*,4*S*,5*S*)-(+)-5-(2,2-Dichloroacetamido)-2-phenyl-4-(4-nitrophenyl)-1,3-dioxanes (**3**).

Compound **3** was obtained in 65% yield, mp 102.7-103 °C; $[\alpha]_D^{21}$ +28.6, ms (m/z): 409(M-1), 394, 380, 327, 305, 259, 241, 176, 153; ir (potassium bromide): 3303(NH), 1675(C=O), 1605, 1520, 1348(NO_2), 1100(C-O-C) cm^{-1}; ^1H nmr (acetone-d_6): δ 4.20 (m, 1, H5), 4.45 (m, 2H, H6), 5.57 (s, 1H, H4), 5.92 (s, 1H, H2), 6.23(s, 1H, $CHCl_2$), 7.36-7.58 (m, 5H, Ar), 7.60-8.20(m, 5H, Ar & NH); ^{13}C nmr (deuteriochloroform): δ 47.6, 65.9, 70.6, 78.5, 101.8, 123.5(2C), 125.9 (2C), 126.5(2C), 128.5(2C), 129.5, 136.9, 144.2, 147.5, 163.6.

Anal. Calcd. for $C_{18}H_{16}N_2O_5Cl_2$(411.24): C, 52.57; H, 3.92; N, 6.81. Found: C, 52.55; H,3.90; N, 6.80.

(2*R*,4*S*,5*S*)-(+)-5-(2,2-Dichloroacetamido)-2-(2-hydroxyphenyl)-4-(4-nitrophenyl)-1,3-dioxanes (**4**).

Compound **4** was obtained in 72% yield, mp 101-102.5 °C; $[\alpha]_D^{21}$+38.0, ms (m/z): 426(M), 390, 305, 291, 275, 241, 221, 191, 170, 153; ir (potassium bromide): 3415(OH), 3308(NH), 1677(C=O), 1605, 1521, 1349(NO_2), 1088(C-O-C) cm^{-1}; ^1H nmr (acetone-d_6): δ 4.20 (m, 1H, H5), 4.52 (m, 2H, H6), 5.58 (s, 1H, H4), 6.18 (s, 1H, H2), 6.24 (s, 1H, $CHCl_2$), 6.92-7.28 (m, 4H, Ar), 7.64-8.20 (m, 5H, Ar & NH), 8.38 (s, 1H, OH); ^{13}C nmr (deuteriochloroform): δ 47.8, 65.9, 70.8, 79.0, 102.2, 117.4, 120.4, 121.4, 123.8(2C), 126.5(2C), 127.6, 131.2, 143.5, 147.8, 154.6, 163.9.

Anal. Calcd. for $C_{18}H_{16}N_2O_6Cl_2$(427.24): C, 50.60; H, 3.77; N, 6.56. Found: C, 50.60; H, 3.77; N, 6.60.

(2*R*,4*S*,5*S*)-(+)-2-(2-Chlorophenyl)-5-(2,2-dichloroacetamido)-4-(4-nitrophenyl)-1,3-dioxanes (**5**).

Compound **5** was obtained in 70% yield, mp 79.5-79.9 °C; $[\alpha]_D^{21}$ +31.0, ms (m/z): 443(M-1), 428, 414, 361, 330, 317, 305, 207, 153; ir (potassium bromide): 3296(NH), 1674(C=O), 1604, 1519, 1349(NO_2), 1100(C-O-C); ^1H nmr (acetone-d_6): δ 4.20 (m, 1, H5), 4.51 (m, 2H, H6), 5.65 (s, 1H, H4), 6.16 (s, 1H, H2), 6.22 (s, 1H, $CHCl_2$), 7.40-7.86 (m, 4H, Ar), 7.66-8.18 (m, 5H, Ar & NH); ^{13}C nmr (deuteriochloroform): δ 47.5, 66.0, 70.9, 79.148, 100.1, 123.5(2C), 126.6(2C), 127.1, 127.8, 130.1, 130.8, 132.8, 134.2, 143.9, 147.6, 163.6.

Anal. Calcd. for $C_{18}H_{15}N_2O_5Cl_3$(445.69): C, 48.51; H, 3.39; N, 6.29. Found: C,48.50; H,3.41; N, 6.32.

(2*R*,4*S*,5*S*)-(+)-(2,2-Dichloroacetamido)-2-(3-nitrophenyl)-4-(4-nitrophenyl)-1,3-dioxanes (**6**).

Compound **6** was obtained in 75% yield; mp 178-179°C; $[\alpha]_D^{21}$ +21.2; ms (m/z): 454(M-1), 439, 425, 409, 391, 372, 355, 341, 325, 304, 221, 153; ir (potassium bromide): 3359(NH), 1714(C=O), 1603, 1521, 1348(NO_2), 1106(C-O-C); ^{1}H nmr (acetone-d_6): δ 4.26 (m, 1H, H5), 4.60 (m, 2H, H6), 5.66 (s, 1H, H4), 6.09 (s, 1H, H2), 6.16 (s, 1H, $CHCl_2$), 7.68-8.00 (m, 4H, Ar), 7.80-8.38 (m, 5H, Ar&NH); ^{13}C nmr (deuteriochloroform): δ 47.6, 65.9, 70.8, 79.2, 100.1, 121.2, 123.6(2C), 124.3, 126.6(2), 129.6, 132.1, 138.9, 143.7, 147.6, 148.1, 163.7.

Anal. Calcd. for $C_{18}H_{15}N_3O_7Cl_2$ (456.24): C, 47.39; H, 3.31; N, 9.21. Found: C, 47.40; H, 3.31; N, 9.27.

(2*R*,4*S*,5*S*)-(+)-5-(2,2-Dichloroacetamido)-2-(4-methyloxyphenyl)-4-(4-nitrophenyl)-1,3-dioxanes (**7**).

Compound **7** was obtained in 85% yield; mp 181-181.5 °C; $[\alpha]_D^{21}$ +25.7; ms (m/z): 440, 404, 368, 357, 289, 274, 256, 236, 191, 153; ir (potassium bromide): 3399(NH), 1705(C=O), 1614, 1518, 1354(NO_2), 1245, 1099(C-O-C); ^{1}H nmr (acetone-d_6): δ 3.80(s, 3H, CH_3), 4.20(m, 1H, H5), 4.44 (m, 2H, H6), 5.55 (s, 1H, H4), 5.90 (s, 1H, H2), 6.25 (s, 1H, $CHCl_2$), 7.00-7.50 (m, 4H, Ar), 7.70-8.20 (m, 5H, Ar & NH); ^{13}C-NMR (deuteriochloroform): δ 47.6, 55.4, 65.9, 70.6, 78.9, 101.9, 113.9(2C), 123.5(2C), 126.6(2C), 127.3(2C), 129.4, 144.2, 147.6, 160.5, 163.6.

Anal. Calcd. for $C_{19}H_{18}N_2O_6Cl_2$ (441.27): C, 51.72; H, 4.11; N, 6.35. Found: C,51.70; H,4.11; N, 6.36.

(2*R*,4*S*,5*S*)-(+)-5-(2,2-dichloroacetamido)-2-furyl-4-(4-nitrophenyl)-1,3-dioxanes (**8**).

Compoud 8 was obtained in 70% yield; mp 74.5-75 °C; $[\alpha]_D^{21}$ +26.3 (c 0.0092g/ml, acetic ester); ir (potassium bromide): 3351(NH), 1689(C=O), 1605, 1522, 1351(NO_2), 1245, 1096(C-O-C); ms (m/z):401, 317, 305, 274, 249, 221, 213, 164, 153; ^{1}H nmr (deuteriochloroform): 4.28 (m, 2H, H6), 4.44 (m, 1H, H5), 5.26 (s, 1H, H4), 5.64 (s, 1H, H2), 5.85 (s, 1H, $CHCl_2$), 6.40 (m, 1H, -C*H*=CH-O-), 6.53(d, 1H, =CH-), 7.19(d, 1H, =CH-O-), 7.44-8.20 (m, 5H, Ar & NH); ^{13}C-nmr (deuteriochloroform): δ 47.6, 65.9, 70.7, 78.9, 108.5, 110.5, 123.5(2C), 126.6(2C), 128.3, 143.1, 143.8, 147.6, 149.4, 163.7.

Anal. Calcd. for $C_{16}H_{14}N_2O_6Cl_2$ (401.20): C, 47.90; H, 3.52; N, 6.98. Found: C, 47.87; H, 3.51; N, 6.99.

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