Synthesis of Regioisomeric Azidobutanediols

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Abstract: Investigations to control the regioselectivity during the acetalization of pivalaldehyde (7) with butane-1,2,4-triol (4) were performed. Thermodynamic control led to the regioisomeric acetals 8 and 9 in the ratio 76:24, whereas kinetic control favored the five-membered acetal 9 (8/9 30:70). Tosylation, nucleophilic substitution with NaN₃, and subsequent methanolysis of the regioisomeric acetals 8 and 9 provided the regioisomeric 4-azidobutanediols 5 and 6, which are considered as valuable building blocks for the synthesis of novel NMDA-receptor antagonists.

Keywords: acetals, azides, regioselectivity, medicinal chemistry, NMDA-antagonists

Recently, we reported the synthesis of the benzophenone acetals 2 and 3, which are derived from the NMDA-receptor antagonist dexoxadrol (1).1-3 Both primary amines 2 and 3 display NMDA-receptor affinity in the low micromolar range.4

Figure 1

The synthesis of 2 and 3 proceeded by regioselective transacetalization of benzophenone dimethyl acetal with butane-1,2,4-triol (4).4 In order to obtain and pharmacologically evaluate further analogues of 2 and 3 with different residues in position 2, non-symmetrically substituted ketones were employed. In addition to the regiochemistry the stereochemistry has to be controlled during transacetalization of non-symmetrically substituted ketone acetals with butane-1,2,4-triol (4). Therefore, we envisaged the synthesis of regioisomeric 4-azidobutanediols 5 and 6, which should be employed as building blocks for the synthesis of various 4-aminoalkyl-1,3-dioxanes and -1,3-dioxolanes, respectively.

A reaction sequence involving 4-azidobutane-1,2-diol (6) as an intermediate is known in the literature.5 Thereby, acetone was reacted with butane-1,2,4-triol (4) to yield regioselectively 2-(2,2-dimethyl-1,3-dioxolan-4-yl)ethanol, which was transformed with p-toluenesulfonyl chloride and sodium azide into the corresponding 4-(2-azidoethyl)-1,3-dioxolane. Hydrolysis of this acetonide with aqueous acetic acid led to the 4-azidobutane-1,2-diol (6), which was oxidatively cleaved with NaIO₄ to afford 3-azidopropanal. Spectroscopic and analytical data of the intermediate 6 were not given, since 6 was not isolated and characterized.

The regioisomeric 4-azidobutane-1,3-diol (5) has not been described so far.

It is well known, that thermodynamically controlled acetalization of polyols with aldehydes leads predominantly to six-membered acetals (1,3-dioxanes), whereas ketones prefer the formation of five-membered acetals (1,3-dioxolanes).6 For the synthesis of 4-azidobutane-1,3-diol (5) six-membered acetals were required. According to the literature the reaction of butane-1,2,4-triol (4) with benzaldehyde or benzaldehyde dimethyl acetal provides predominantly (>90%) the six-membered acetal.7 However, after transformation of the residual OH-group into the desired N₃-moiety the acetal should be cleaved. Since it seemed difficult to separate the stochiometric side product benzaldehyde or its acetal from the polar 4-azidobutane-1,3-diol (5) the volatile pivaldehyde (7) was used instead of benzaldehyde. The reaction of pivaldehyde (7) with butanetriol 4 at room temperature for 29 hours provided the regioisomeric acetals 8 and

Figure 2
9 in the ratio 30:70 (Table 1, line 1). Prolonging the reaction time or raising the reaction temperature shifted the ratio in favor of the six membered 1,3-dioxane 8 (Table 1). The regioisomeric acetals 8 and 9 were separated by flash chromatography. Subsequently, the isolated and purified acetals 8 and 9 were dissolved in THF, a catalytic amount of p-toluenesulfonic acid was added and the reaction mixture was heated to reflux. After 70 hours the thermodynamically controlled equilibrium was reached and both experiments revealed that 8 and 9 were formed in the ratio 76: 24, independent of the starting acetal. These experiments demonstrate that the product ratio during acetalization of pivalaldehyde (7) with butane-1,2,4-triol (4) is controlled by the reaction conditions: kinetic control yields predominantly the 1,3-dioxolane 9 whereas thermodynamic control leads to the six-membered acetal 8 as the main product.

The alcohols 8 and 9 were separated and transformed into the azides 12 and 13 by tosylation and subsequent nucleophilic substitution with sodium azide. Cleavage of the pivalaldehyde acetals 12 and 13 was performed by heating a methanolic solution of 12 and 13 with a strongly acidic cation exchange resin (Amberlyst® 15). After complete transformation it was filtered and the volatile components, including pivalaldehyde dimethyl acetal, were removed in vacuo. The residues contained pure 4-azidobutane-1,3-diol (5, yield 73%) and 4-azidobutane-1,2-diol (6, yield 78%) respectively.

Whereas the described acetalization provided only the cis-diastereomer of the six-membered acetal 8, both diastereomers of the five-membered acetal cis-9 and trans-9 were formed. At room temperature (kinetic control, line 1) the ratio cis-trans-9 was 86:14, whereas heating of the reaction mixture led to an increased production of trans-9 (cis-trans-9 60:40).

The analogous methanolysis of the azidoethyl substituted acetonide 14 using the strongly acidic cation-exchange resin Amberlyst® 15 and evaporation of the volatile dimethyl acetal of acetone provided the 4-azidobutane-1,2-diol (6) in almost quantitative yield (99%).

The regioisomeric 4-azidobutanediols 5 and 6 represent valuable building blocks for the synthesis of novel NMDA-receptor antagonists related to dexoxadrol (1).

Unless otherwise noted, moisture sensitive reactions were conducted under dry nitrogen. Petroleum ether used refers to the fraction boiling at 40–60 °C. TLC: Silica gel 60 F 254 plates (Merck). Flash chromatography (fc): Silica gel 60, 0.040–0.063 mm (Merck); parentheses include: diameter of the column (cm), eluent, fraction size (mL). Elemental analyses: Vario EL (Elementaranalysesysteme GmbH). MS: MAT 312, MAT 8200, MAT 44, and TSQ 7000 (Finnigan); IR: IR spectrophotometer 1605 FT-IR (Perkin-Elmer). 1H NMR (300 MHz), Unity 300 FT NMR spectrometer (Varian), δ in ppm relative to TMS, coupling constants are given with 0.5 Hz resolution.
residue was suspended in EtOAc (30 mL), filtered, the filtrate was washed with an aq sat. solution of NaHCO₃ (15 mL), dried (MgSO₄) and concentrated in vacuo. After recording a ¹H NMR spectrum the residue was purified by fc (6 cm, petroleum ether—EtOAc 7:3, 20 mL fractions).

8

Yield: 0.288 g (33%); R; 0.29; colorless oil.

IR (film): 3416 (OH), 2959 (CH), 2864 (CH), 1140, 1115 (CO) cm⁻¹.

¹H NMR (CDCl₃): δ = 0.91 [s, 9 H, C(CH₃)₃], 1.31 (dd, J = 13.1, 2.6, 1.5 Hz, 1 H, 5-Haxial), 1.72 (ddddd, J = 13.1, 12.5, 11.3, 5.2 Hz, 1 H, 5-Hequat), 1.97 (br s, 1 H, OH), 3.55 (dd, J = 11.6, 6.7 Hz, 1 H, CH₂OH), 3.63 (dd, J = 11.6, 3.4 Hz, 1 H, CH₂OH), 3.71 (ddd, J = 12.5, 11.3, 2.7 Hz, 1 H, 6-Haxial), 3.75 (ddt, J = 11.3, 6.7, 3.0 Hz, 1 H, 4-Haxial), 4.13 (ddd, J = 11.3, 5.2, 1.5 Hz, 1 H, 6-Hequat), 4.14 (s, 1 H, 2-Haxial).

MS (Cl, NH₃): m/z (%) = 192 (M + NH₃, 36), 175 (M + H, 17), 86 (Me₃CCHO, 100).

Anal. Calcd for C₆H₁₂O₇ (348.22): C, 58.5; H, 7.37; S, 9.76. Found: C, 58.6; H, 7.31; S, 10.01.

(2)-cis- and trans-2-(2-tert-Butyl-1,3-dioxol-4-yl)ethyl p-Toluene sulfonate (11)

A cooled solution of p-TsCl (1.525 g, 8 mmol) in CH₂Cl₂ (10 mL) was added to a cooled solution of 9 (cis-trans-9 66:34, 0.697 g, 4 mmol) and Et₃N (0.67 mL, 4.8 mmol) in CH₂Cl₂ (30 mL) and the mixture was stirred for 48 h at 4°C. The solvent was evaporated in vacuo and the residue was purified by fc (6 cm, petroleum ether—EtOAc 9:1, 35 mL fractions). The ratio of cis-trans-11 was 66:34.

Yield: 0.959 g (73%); R; 0.14; colorless solid; mp 51.5–53 °C.

IR (KBr): 2960 (CH), 2870 (CH), 1356, 1175 (SO₃), 1115 (CO), 814 (aryl) cm⁻¹.

¹H NMR (CDCl₃): δ = 0.90 [s, 9 x 0.34 H, C(CH₃)₃], 0.91 [s, 9 x 0.66 H, C(CH₃)₃], 1.91 (dtd, J = 14.3, 7.9, 5.5 Hz, 0.66H, CH₂CH₂OTos), 1.90–1.97 (m, 2 x 0.34 H, CH₂CH₂OTos), 1.99 (dddd, J = 14.3, 7.6, 6.7, 4.6 Hz, 0.66H, CH₂CH₂OTos), 2.51 (s, 3 H, PhCH₃), 2.48 (dd, J = 7.3, 6.1 Hz, 0.34 H, 5-H), 3.54 (dd, J = 7.8, 6.0 Hz, 0.34H, 5-H), 3.95 (dd, J = 7.8, 6.6 Hz, 0.66 H, 5-H), 4.10 (dd, J = 7.3, 5.5 Hz, 0.34H, 5-H), 4.12 (dd, J = 7.9, 4.1 Hz, 0.66H, 4-H), 4.13 (quint., J = 5.8 Hz, 0.34H, 4-H), 4.20–4.26 (m, 2 x 0.34 H, CH₂CH₂OTos), 4.21 (dd, J = 11.6, 7.6, 5.5 Hz, 0.66 H, CH₂CH₂OTos), 4.25 (dd, J = 11.6, 6.7, 5.5 Hz, 0.66 H, CH₂CH₂OTos), 4.51 (s, 0.66H, 2-H), 4.57 (s, 0.34H, 2-H), 7.41 (d, J = 8.2 Hz, 2 H, Ar3-H, 5-HpHCH), 7.86 (d, J = 8.2 Hz, 2 H, Ar2-H, 6-HpHCH).

MS (Cl, NH₃): m/z (%) = 346 (M + NH₃, 100), 329 (M + H, 14), 86 (Me₃CCHO, 26).

Anal. Calcd for C₆H₁₂O₅S (328.42): C, 58.5; H, 7.37; S, 9.76. Found: C, 58.3; H, 7.34; S, 10.20.

(±)-cis-4-(Azidomethyl)-2-tert-butyl-1,3-dioxane (12)

A solution of 10 (0.755 g, 2.3 mmol) and NaN₃ (1.495 g, 23 mmol) in DMF (30 mL) was heated to reflux for 2 h. The solvent was removed in vacuo and the residue was suspended in EtO (30 mL). The mixture was washed with an aq sat. solution of NaHCO₃ (15 mL, water (15 mL), dried (MgSO₄), and concentrated in vacuo to give pure 12.

Yield: 0.374 g (82%); colorless oil.

IR (film): 2960 (CH), 2861 (CH), 2100 (N), 1140, 1114 (CO) cm⁻¹.

¹H NMR (CDCl₃): δ = 0.90 [s, 9 H, C(CH₃)₃], 1.33 (dtd, J = 13.1, 2.4, 1.4 Hz, 1 H, 5-HpHCH), 1.71 (dtd, J = 13.1, 12.2, 11.6, 5.2 Hz, 1 H, 5-HpHCH), 3.10 (ddd, J = 12.8, 3.4 Hz, 1 H, CH₃N), 3.27 (dd, J = 12.8, 7.0 Hz, 1 H, CH₃N), 3.70 (ddd, J = 12.2, 11.6, 2.4 Hz, 1 H, 6-HpHCH), 3.83 (ddd, J = 11.6, 7.0, 3.4, 2.4 Hz, 1 H, 4-HpHCH), 4.12 (s, 1 H, 2-HpHCH), 4.13 (d, J = 11.6, 5.2, 1.4 Hz, 1 H, 6-HpHCH).

MS (Cl, NH₃): m/z (%) = 217 (M + NH₃, 0.7), 172 (M + H – N₂, 100), 86 (Me₃CCHO, 48).


(±)-cis- and (±)-trans-2-(2-Azidoethyl)-1,3-dioxane (13)

A solution of 11 (cis-trans-11 66:34, 98.5 mg, 0.3 mmol) and NaN₃ (0.195 g, 3 mmol) in DMF (5 mL) was heated to reflux for 1.5 h. The solvent was removed in vacuo and the residue was suspended in EtO (5 mL). The suspension was washed with an aq sat. solution of NaHCO₃ (5 mL) and water (5 mL), dried (MgSO₄), and concentrated in vacuo. The ratio of cis-trans-13 was 66:34.

Colorless oil, yield 46.5 mg (78%).

IR (film): 2959 (CH), 2872 (CH), 2099 (N), 1112 (CO) cm⁻¹.
1H NMR (CDCl₃): δ = 0.91 [s, 9 × 0.34 H, C(CH₃)₃], 0.93 [s, 9 × 0.66 H, C(CH₃)₃], 1.68–1.93 (m, 2 × 0.34 H, CH₂CH₃N₃), 1.80 (dd, J = 13.7, 7.0, 5.5 Hz, 0.66 H, CH₂CH₃N₃), 1.85 (dd, J = 13.7, 7.0, 5.8 Hz, 0.66 H, CH₂CH₃N₃), 3.42–3.48 (m, 2 × 0.34 H, C₃H₂N₃), 3.43 (dt, J = 7.6, 6.3 Hz, 0.66 H, CH₂CH₃N₃), 3.48 (dd, J = 7.3, 6.4 Hz, 0.34 H, 5-H), 3.50 (dd, J = 7.3, 6.4 Hz, 0.34 H, 5-H), 3.97 (dd, J = 7.6, 6.7 Hz, 0.66 H, 5-H), 4.07–4.12 (m, 0.34 H, 5-H), 4.09–4.17 (m, 0.34 H, 4-H), 4.13 (tdd, J = 7.0, 6.3, 5.5 Hz, 0.66 H, 4-H), 4.56 (s, 0.66 H, 2-H), 4.62 (s, 0.34H, 2-H).

MS (CI, NH₃): m/z (%) = 217 (M + NH₄, 1), 172 (M + H - N₂, 100), 86 (Me₃CCHO, 21).


(±)-4-Azidobutan-1,3-diol (5)
A mixture of 12 (0.10 g, 0.5 mmol), strongly acidic ion-exchange resin (Amberlyst® 15, 50 mg) and MeOH (5 mL) was heated to reflux for 2.5 h. The volatile components were evaporated in vacuo, MeOH (5 mL) was added to the residue and the mixture was heated to reflux for an additional 2.5 h. This procedure was repeated three times. Finally, the mixture was concentrated in vacuo, CH₂Cl₂ (5 mL) was added to the residue, the CH₂Cl₂ layer was dried (MgSO₄), filtered through Celite® AFA and concentrated in vacuo to yield the azidobutanediol 5.

Yield: 48.1 mg (73%); colorless oil.
IR (film): 3358 (OH), 2937 (CH), 2104 (N₃), 1054 (CO) cm⁻¹.

1H NMR (CDCl₃): δ = 1.72 (ddt, J = 14.6, 6.1, 4.4 Hz, 1 H, 2-H), 1.78 (dddd, J = 14.6, 8.2, 7.2, 4.6 Hz, 1 H, 2-H), 2.36 (s, 2 H, OH), 3.32 (dd, J = 12.5, 7.0 Hz, 1 H, 4-H), 3.40 (dd, J = 12.5, 4.3 Hz, 1 H, 4-H), 3.86 (dd, J = 10.7, 7.2, 4.6 Hz, 1 H, 1-H), 3.92 (dd, J = 10.7, 6.1, 4.6 Hz, 1 H, 1-H), 4.01 (dd, J = 8.2, 7.0, 4.3 Hz, 1 H, 3-H).

(±)-4-Azidobutane-1,2-diol (6)
Method a:
A mixture of 13 (0.199 g, 1 mmol), strongly acidic ion exchange resin (Amberlyst® 15, 50 mg) and MeOH (15 mL) was stirred for 5 h at r.t. The mixture was filtered and the filtrate was concentrated in vacuo to yield 5 (0.195 g, 99%).

Method b:
A mixture of 14 (0.257 g, 1.5 mmol), strongly acidic ion exchange resin (Amberlyst® 15, 150 mg) and MeOH (15 mL) was stirred for 5 h at r.t. The mixture was filtered and the filtrate was concentrated in vacuo to yield 5 (0.219 g, 99%).

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