Convenient Synthesis of Chiral 5-Amino-1,3-Dioxanes Built on Some *l-p*-Nitrophenylserinols Skeletons

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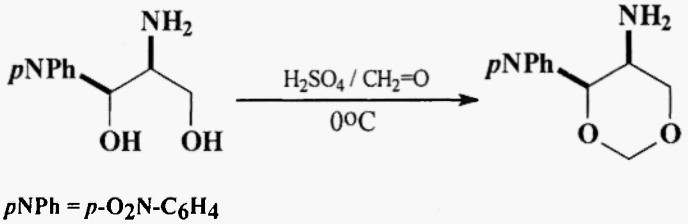
Abstract: a simple and rapid methodology for the synthesis of the title compounds is described in order to access polychiral (enantiomerically pure) 5-aminodioxanes in satisfactory yields. The reaction of two nitrophenylserinols with two versatile carbonyl electrophiles (formaldehyde and glyoxal) in very strong acidic conditions (96% H_2SO_4) is discussed together with the limitations of the method.

INTRODUCTION

(1*R*,2*R*)-2-Amino-1-(4-nitrophenyl)-propane-1,3-diol (better known by its trivial name as issued from pharmaceutical chemistry as *threo-p*-Nitrophenylserinol) was long time considered only in connection to its N-dichloroacetamido derivative, Chloromycetine®. We already reviewed the chemistry of the heterocyclic saturated systems involved as precursors of *p*-nitrophenylserinol and called attention about the major difference between the reactivity of the latter and that of phenylserinol itself.[1] On the other hand, only few methods are known to access enantiomerically pure 5-amino-1,3-dioxanes by direct ring closure of the corresponding 2-amino-1,3-propanediols. One of these methods, successfully developed by our group, consisted in the treatment of the *l-p*-nitrophenylserinol (as its 1*S*,2*S* enantiomer) with formaldehyde in the presence of an excess of concd. H_2SO_4 to afford only the corresponding (4*S*,5*S*)-5-amino-4-(4-nitrophenyl)-1,3-dioxane in 75% yield (**Scheme 1**).[2]

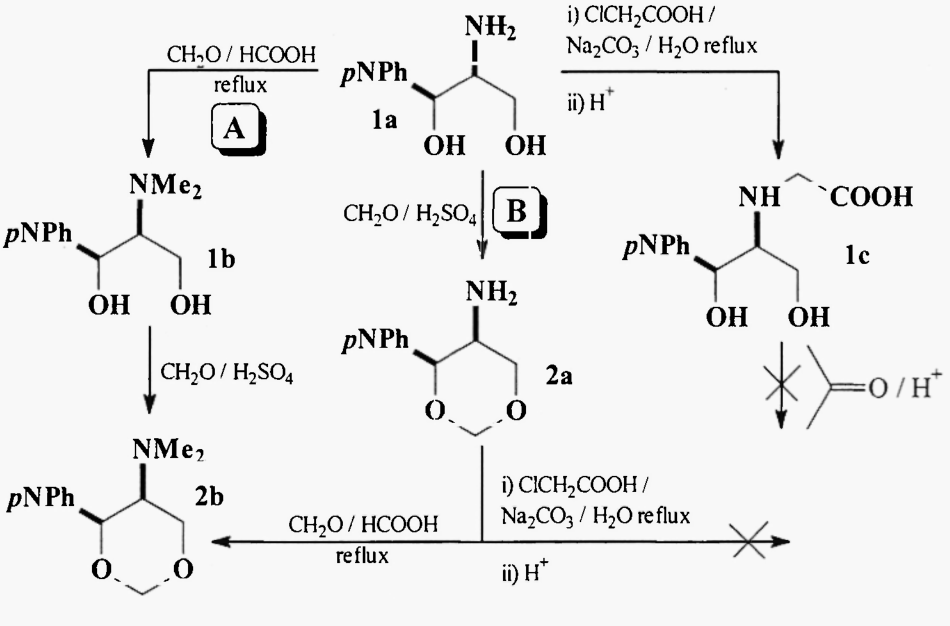


Scheme 1

In our previous research, the above selective cancellation of nucleophylicity of *p*-nitrophenylserinol (**Scheme 1**) allowed us, recently, the complete diastereoselective synthesis of various 1,3-dioxanic Schiff-bases built on its skeleton and, in a more general approach, to describe in terms of ring-chain tautomerism, such type of cyclocondensation.[3-7] In this paper, it is our intention to enlarge the area of the investigation towards more complex 1,3-dioxane structures by direct ring closure of the appropriate *p*-nitrophenylserinols. Preliminary results are hereafter discussed.

RESULTS AND DISCUSSION

The chemistry we followed is depicted in **Scheme 2** and **3**. All synthesis started from enantiomerically pure (1*S*,2*S*)-*p*-nitrophenylserinol, **1a**.

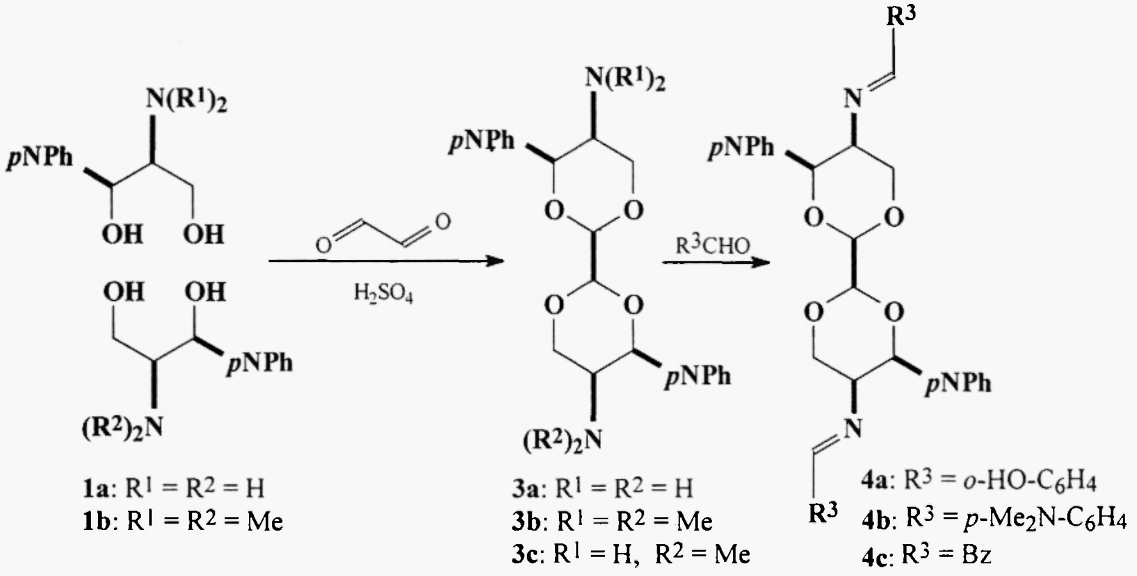


Scheme 2

The synthesis of N-substituted *p*-nitrophenylserinols **1b**, **c** was easily achieved in good yields; thus, **1b** was prepared following the literature data[8,9] in a Leuckart-Wallach type reaction (70% yield). Then, the glycine derivative **1c** was obtained by a classic method (67% yield). Although similar enough with other biological buffers (*e.g.* TRIS® and TRICINE®),[10] we were surprised that this compound had been previously unknown. Unfortunately, both **1b**, **c** revealed very poor (or no) reactivity against ketalisation. Different conditions, generally recommended in the literature,[11] together with special ones (*e.g.* P_2O_5 / THF)[12,13] exhibited only some minor evolution of the reaction (TLC monitoring). Accordingly, the work-up of the crude reaction mixtures afforded the starting materials **1b**, **c** in almost quantitative yield. Therefore, we considered as appropriate the conditions previously described by us for the synthesis of the aminodioxane **2a**.[2] Indeed (**Scheme 2**, route A) treatment of dimetilaminoderivative **1b** in concd. (96%) H_2SO_4 (1 : 10 molar ratio respectively) with equimolar amount of paraformaldehyde at 0°C yielded the new compound **2b** in 55% yield in a very clean reaction (overall yield 39% against **1a**). In an alternative pathway (**Scheme 2**, route B), the aminodioxane **2a** was submitted to Leuckart-Wallach conditions to afford **2b** in 67% yield (overall yield 50% with respect to **1a**). Attempt at N-alkylation of **2a** (*e.g.* with monochloroacetic acid to access the simplest ketal of **1c**) surprisingly failed since, in our hands, other trivial functionalisations of the same compound (as N-acylation and Schiff-bases) had been successfully carried out.[3,4 - 7] We note that the protocol described above was not appropriate for the glycine derivative **1c** whose ring closure (if really took place, **Scheme 2**) afforded unstable products since constantly the starting material was recovered.

Keeping in mind that only very strong acid conditions are to be hereafter considered, the selection regarding another possible carbonyl partner focused on glyoxal. Obviously, our choice was supported by the absence of a α-methylene group, in order to avoid trivial crotonisations. In connection with this crucial requirement, we emphasise that the behaviour against *p*-nitropenylserinol, in similar conditions of certain aryl aldehydes was previously examined by our group.[7]

The chemistry is shown in **Scheme 3**.



1a: $R^1 = R^2 = H$
1b: $R^1 = R^2 = Me$

3a: $R^1 = R^2 = H$
3b: $R^1 = R^2 = Me$
3c: $R^1 = H$, $R^2 = Me$

4a: $R^3 = o\text{-HO-}C_6H_4$
4b: $R^3 = p\text{-}Me_2N\text{-}C_6H_4$
4c: $R^3 = Bz$

Scheme 3

To the best of our knowledge, both chemistry and all compounds **3**, **4** are new ones.

Preliminary attempts based on classical methods[11] (*e.g.* refluxing the *p*-nitrophenylserinols **1a, b** with glyoxal in a 2 : 1 molar ratio respectively, in aromatic solvent and removing the water in a Dean-Stark trap) provided crude reaction mixtures which revealed complex NMR spectra.[14] Therefore, we emerged to the same methodology, able to ensure a better chemioselectivity, similar to formaldehyde. Thus, slowly addition of glyoxal to the nitrophenylserinol **1a** in 96% H_2SO_4 at 0°C yielded the 2,2'-1,3-dioxane dimer **3a** in 33% yield meanwhile the same procedure in the case of **1b** afforded **3b** with a comparative result (35% yield). However, the "cross-coupling" as dioxane dimer between **1a** and **1b** gave poor selectivity, as a mixture **3a** : **3b** : **3c** = 39% : 15% : 46% after column chromatography (molar conversion 29% for **1a** and 17% for **1b**, yield 11% with respect to **3c**). No epimerization was detected in all cases and complete *2R,2'R* diastereoselectivity was clearly revealed by COSY and ROESY NMR experiments regarding the new chiral center thus created.

Although optimisation of this synthesis is still under exploring, preliminary investigation of reactivity concerning dimers **3** showed the expected selectivity: the double dioxane Schiff bases **4** were prepared with excellent yields (90% **4a**, 84% **4b** and 83% **4c**) and complete *E,E*-diastereoselectivty. Then, the option to use certain aldehydes as salicylaldehyde (in the case of **4a**) and 4-dimethylaminobenzaldehyde (for **4b**) in reaction with dimer **3a** was based on our previous results focused on the problem of ring-chain tautomerism of simple Schiff-bases of **1a**.[6] Thus, analogous acyclic 2-benzylideneamino derivatives of **1a** (derived from salicylaldehyde and 4-dimethylaminobenzaldehyde) had been shown as authentic stable forms as Schiff-bases. However, in the present study, treatment of these Schiff-bases with glyoxal, as an alternative route to prepare dimers **4a**, **b**, failed: the TLC monitoring indicated no chemioselectivity as confirmed by NMR spectra of the crude reaction mixtures.[14]

Finally, we note that the chemistry discussed in this paper seems to be not promising for phenylserinol itself. Indeed, in the same conditions, it has exhibited only decomposition of the reaction mixtures. This might be explained by its facility to epimerize *via* a benzyle carbocation which could also promote, at this stage of our knowledge, unpredictable evolution.

CONCLUSIONS

Chiral enantiomerically pure 5-amino-1,3-dioxanes (as single unit or 2,2'-dimers) are readily available by ring closure of certain *p*-nitrophenylserinols in strong acidic media in reaction with formaldehyde and glyoxal. No epimerization is detected. The resulted compounds allow further N-functionalisation as Leuckart-Wallach type reaction and 1,3-dioxanic Schiff-bases.

EXPERIMENTAL

The main data concerning the prepared compounds are listed in **Table 1.**

Melting points were are not corrected. NMR spectra were recorded on VARIAN GEMINI 300 instrument operating at 300 and 75MHz for ^{1}H and ^{13}C nuclei and Brucker AM400 instrument operating at 400 and 100MHz for ^{1}H and ^{13}C nuclei. No $SiMe_4$ was added; chemical shifts were measured against the solvent peak. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck®); flash column chromatography was conducted on Silica gel Si 60 (40 - 63μm, Merck®). The synthesis of the compound **2a** was described elsewhere.[2] All new compounds **1c**, **2b**, **3**, **4** yielded satisfactory elemental analysis. Specific rotations were performed on Jasco DIP-1000 Instrument.

Typical procedure for Leuckart-Wallach reaction; preparation of (4*S*,5*S*)-5-Dimethylamino-4-(4-nitrophenyl)-1,3-dioxane, 2b; (4*S*,5*S*)-5-amino-4-(4-nitrophenyl)-1,3-dioxane **2a** (5.00g, 22mmol), formic acid (86%, 3.22g, 4.1mL, 70mmol) and paraformaldehyde (1.98g, 66mmol) were stirred for 2hrs on a steam bath. After cooling at room temperature, the reaction mixture was poured in cooled water (25mL) then neutralised with 15% aq. NaOH (about 12mL). The resulted crystalline solid was filtered off, washed with water to neutrality and recrystallized from methanol (60mL) to yield 3.70g of the desired product **2b**.

Typical procedure to prepare the dimers 3; preparation of (2*R*,2'*R*,4*S*,4'*S*,5*S*,5'*S*)-5-Dimethylamino-4-(4-nitrophenyl)-2-[5'-amino-4'-(4'-nitrophenyl)-1',3'-dioxan-2'-yl]-1,3-dioxane, 3c; glyoxal monohydrate (1.83g, 24.06mmol) was suspended in concd. sulphuric acid (96%, 24.56g, 13.35mL, 240.6mmol) with vigorous stirring and cooled at 0°C. (1*S*,2*S*)-2-Amino-1-(4-nitrophenyl)-propane-1,3-diol **1a** (as hydrochloride, 6.00g, 24.06mmol) was then added portionwise (5 x 1.20g, each 3hrs.) at 0°C. The reaction mixture was diluted with additionally concd. sulphuric acid (96%, 24.56g, 13.35mL, 240.6mmol) at 0°C. (1*S*,2*S*)-2-Dimethylamino-1-(4-nitrophenyl)-propane-1,3-diol **1b** (5.80g, 24.06mmol) was finally added and the reaction mixture was let to stir and reach the room temperature over night. The mixture was carefully neutralized at 0°C with dichloromethane (300mL), and 1:1 aq. NH_3 (200mL 25% NH_3 and 200g ice). The organic layer was filtered off, washed with water to neutrality, dried over $CaCl_2$ and evaporated *in vacuo*. The resulted crude solid (3.70g) was separated by flash column chromatography (80g SiO_2, eluent MeOH : dichloromethane 3 : 1 v/v) to yield the following three fractions: **3b** (0.40g), **3c** (1.20g) and **3a** (1.00g). Each fraction was crystallized from ether.

Table 1 : Relevant data of the synthesis of compounds **1b, c, 2 - 4.**

No.	Yield (%)	m.p. (°C)	$[\alpha]_D^{20}$	Relevant NMR data (δ ppm, *J* Hz)
1b	70	97-8 yellow crystalline powder	+14.77 (1%MeOH)	**^{1}H-NMR** (DMSO-d_6): 8.18 (2H, d, 8.7), 7.65 (2H, d, 8.7), 5.20 (1H, bs), 4.69 (1H, d, 7.5), 4.28 (1H, bs), 3.47 (1H, dd, 11.2, 7.2), 3.38 (1H, dd, 11.2, 4.6), 2.61 (1H, ddd as sextet 7.3, 7.3, 4.7), 2.41 (6H, s) **^{13}C-NMR** (DMSO-d_6): 152.3, 146.4, 128.0, 70.3, 56.9, 41.9
1c	67	213-4 yellow crystalline powder	+28.80 (1%MeOH)	**^{1}H-NMR** (DMSO-d_6): 7.74 (2H, d, 8.1), 7.18 (2H, d, 8.3), 6.25 (2H, bs), 4.33 (1H, d, 7.0), 2.95 (1H, dd, 11.6, 3.8), 2.69 (1H, dd, 11.4, 5.0), 2.49 (1H, d, 4.5), 2.03 (3H, s)
2b	55 (**A**) 67 (**B**)	131-2 yellow crystalline powder	+115.00 (1% $CHCl_3$)	**^{1}H-NMR** ($CDCl_3$): 8.21 (2H, d, 8.7), 7.54 (2H, d, 8.5), 5.28 (1H, d, 6.3), 5.03 (1H, d, 3.0), 4.96 (1H, d, 6.1), 4.55 (1H, d, 12.4), 3.93 (1H, dd, 12.4, 2.7), 2.74 (1H, s), 2.01 (6H, s) **^{13}C-NMR**: 147.4, 126.3, 123.3, 94.1, 81.0, 65.3, 60.2, 43.9
3a	33	141-2 yellowish crystalline powder	-11.50 (1% MeOH)	**^{1}H-NMR** ($CDCl_3$): 8.21 (4H, d, 8.7), 7.51 (4H, d, 8.5), 5.10 (2H, s), 4.98 (2H, s), 4.26 (2H, d, 11.3), 4.21 (2H, d, 11.7), 3.01 (2H, s), 1.40 (4H, bs.) **^{13}C-NMR**: 147.3, 146.1, 126.5, 123.7, 100.1, 80.2, 73.1, 49.7
3b	35	123-4 yellowish crystalline powder	-12.14 (1% MeOH)	**^{1}H-NMR** ($CDCl_3$): 8.21 (4H, d, 8.5), 7.54 (4H, d, 8.3), 5.19 (2H, d, 3.4), 5.01 (2H, s), 4.70 (2H, d, 12.5), 4.07 (2H, dd, 12.5, 2.9), 2.81 (2H, dd as t, 2.8), 2.35 (12H, s) **^{13}C-NMR**: 147.0, 126.2, 123.3, 99.8, 80.7, 65.3, 59.3, 43.8

3c	11	134-5 yellowish crystalline powder	-3.18 (1% MeOH)	**^{1}H-NMR** ($CDCl_3$): 8.11 (2H, d, 9.8), 8.08 (2H, d, 9.1), 7.43 (2H, d, 9.0), 7.40 (2H, d, 9.0), 5.06 (1H, d, 2.6), 4.99 (1H, s), 4.91 (1H, d, 4.2), 4.84 (1H, d, 4.1), 4.58 (1H, d, 12.4), 4.15 (1H, d, 11.3), 4.09 (1H, d, 11.3), 3.95 (1H, dd, 12.4, 2.3), 2.91 (1H, s), 2.68 (1H, s), 2.20 (6H, s), 1.42 (2H, bs) **^{13}C-NMR**: 147.7, 147.4, 147.2, 146.4, 126.8, 126.6, 124.1, 123.6, 100.5, 100.2, 81.1, 80.4, 73.4, 65.7, 59.6, 50.1, 44.1
4a	90	200 dec. yellowish crystalline powder	-11.79 (1% $CHCl_3$)	**^{1}H-NMR** ($CDCl_3$): 13.15 (2H, bs), 8.17 (4H, d, 8.3), 8.13 (2H, s), 7.56 (4H, d., 8.3), 7.30 (2H, dd as t, 7.5, 7.1), 7.07 (2H, d, 7.5), 6.93 (2H, d, 8.3), 6.80 (2H, dd as t, 7.1, 7.5), 5.35 (2H, s), 5.26 (2H, s), 4.45 (2H, d, 11.7), 4.35 (2H, d, 11.3), 3.65 (2H, s) **^{13}C-NMR**: 166.7, 161.5, 147.7, 145.5, 133.2, 131.9, 127.3, 124.0, 119.0, 118.7, 117.6, 100.1, 79.8, 71.7, 65.5
4b	84	245-50 orange crystalline powder	-9.52 (1% $CHCl_3$)	**^{1}H-NMR** ($CDCl_3$): 8.01 (4H, d, 9.1), 7.85 (2H, s), 7.45 (4H, d, 8.7), 7.35 (4H, d, 8.7), 6.51 (4H, d, 9.1), 5.22 (2H, d, 1.5), 5.19 (2H, s), 4.33 (2H, d, 12.1), 4.29 (2H, d, 12.4), 3.49 (2H, s), 2.91 (12H, s) **^{13}C-RMN**: 163.0, 152.5, 147.4, 146.7, 130.2, 128.0, 124.3, 123.5, 111.7, 100.2, 80.8, 72.0, 66.1, 40.5
4c	83	163-6 yellowish crystalline powder	-8.21 (1% $CHCl_3$)	**^{1}H-NMR** ($CDCl_3$): 8.06 (4H, d, 8.7), 7.97 (2H, s), 7.75 (4H, d, 7.7), 7.45 (6H, m), 7.23 (4H, dd as t, 7.5, 7.5), 5.32 (2H, s), 5.16 (2H, s), 4.38 (2H, dd, 12.4, 1.89), 4.31 (2H, d, 12.1), 3.83 (2H, s) **^{13}C-NMR**: 190.4, 162.6, 147.7, 145.6, 134.7, 134.2, 130.9, 128.6, 127.2, 123.9, 100.2, 79.3, 71.0, 65.9

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