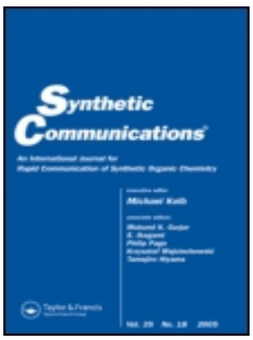

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SYNTHESIS OF SOME SELECTIVELY *N*-PROTECTED (1*S*,2*S*)-*p*-NITROPHENYLSERINOL–BASED DIAMINO-1,3-DIOXANES AND TRIPODANDS

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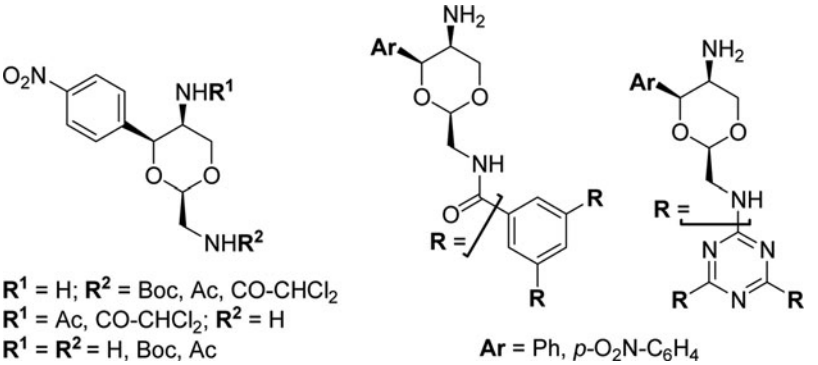
GRAPHICAL ABSTRACT



Abstract *The unconventional methodology for the non-epimerizable cycloacetalization of optically active (1S,2S)-2-amino-1-(4-nitrophenyl)propane-1,3-diol (p-nitrophenylserinol) (condensed H_2SO_4 96% as solvent and catalyst, i.e., sulfuric transacetalization) producing (2R,4S,5S) diamino-1,3-dioxanes was enlarged by the use of N-protected forms of 2,2-dimethoxyethylamine (DMEA, aminoacetaldehyde dimethylacetal). Conversely, N-protected derivatives of p-nitrophenylserinol were successfully cyclocondensed with DMEA in the same sulfuric conditions. N-Functionalization of DMEA upon treatment with trimesic acid trichloride and cyanuric chloride yielded the corresponding triple amide and melamine, respectively. Their adapted sulfuric transacetalization in triplicate in reaction with arylserinols (aryl: phenyl, p-nitrophenyl) afforded a new series of optically active tripodands.*

Keywords Protecting groups; serinols; transacetalization; tripodands

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INTRODUCTION

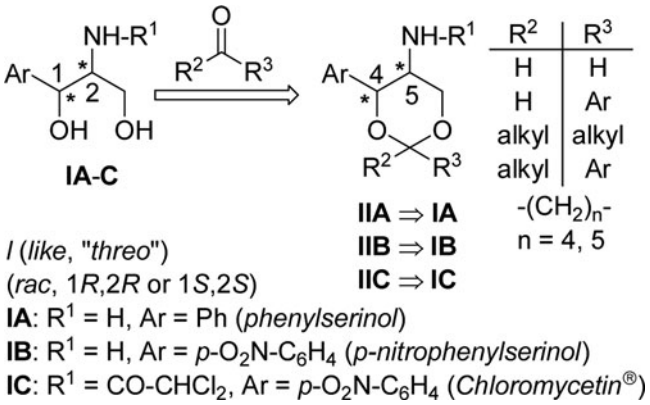
Cycloacetalization of commercial optically active *l*-2-amino-1-arylpropane-1, 3-diols (arylserinols) **IA** and **IB** (Scheme 1) as well as that of *N*-dichloroacetyl-derivative (1*R*,2*R*)-**IC** of **IB**, the antibiotic Chloromycetin,[1,2] has been a challenging task for organic chemists as early as 1950s,[3a] for example (1*R*,2*R*)-**IC** → (4*R*,5*R*)-**IIC** [$R^2 = R^3 =$ Me, $(CH_2)_n$ n = 4, 5 etc].

At that time, 1,3-dioxanes of type (4*R*,5*R*)-**IIC** were seen as prodrugs of Chloromycetin. Their synthesis required strong dehydrating methods using P_2O_5, H_2SO_4,[3a,3b] or concentrated HCl.[3c] Recently, conformational analysis concepts[4a,4b] and NMR data[4c] based studies justified these experimental conditions by the steric hindrance between the *cis* (*gauche*) positioned ligands, eq-C-4 (Ar)/ax-C-5 (HN<), in the ensuing anancomeric condensates **IIA**–**C**. This spatial arrangement originates from (i) the *l* (*like*) configuration of the open-chain precursors **IA**–**C** and (ii) their non-epimerizable, hence diastereospecific, cyclization. Indeed, in the absence of the aryl moiety at C-1 in **IA**–**C** (Scheme 1), cycloacetalization of the resulting *N*-protected 2-aminopropane-1,3-diol (serinol), as well as that of its C-2 substituted analogs, occurs following classical protocols.[5] We mention here the only work of Meslard et al.[6] in 1985, claiming the synthesis of a series of Chloromycetin **IC**–based 1,3-dioxanes **IIC** in mild conditions by using various (non)symmetric carbonyl electrophiles (Scheme 1) with yields ranging between 4 and 89%.

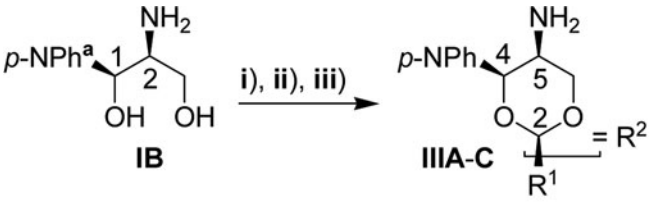
The same ring closure in the case of optically active free amine *l*-**IB**, *p*-nitrophenylserinol, is much less documented. We previously demonstrated this reaction is practicable in the so-called *sulfuric (trans)acetalization* conditions, for example, starting from (1*S*,2*S*)-**IB** (Scheme 2).[7]

This forcing acidic medium was also mandatory to temporarily complete blocked nucleophilicity of the primary amino group of **IB,** thus avoiding any *N*-protection–deprotection step.[2] Our methodology was inspired by the pioneering work of Nagawa in 1955[8] referring to the related reaction between *u* (*unlike, "erythro," rac*)-**IB** and acetone.

Taxing conditions were reported as well for cycloacetalization of *N*-protected forms of (*l, rac* or optically active) phenylserinol **IA** (formyl[9a–9c] and acetyl[9d])



Scheme 1. Previously reported types of arylserinols and Chloromycetin-based 1,3-dioxanes.[1–4,6]



i) 10 equiv. H_2SO_4 (96%) / 0 °C (1 h); **ii)** *n* equiv. (masked) carbonyl electrophile / 0 °C → r.t. (24 h); **iii)** aq. NH_3 (25%) / 0 °C, pH = 10-11

(Masked) carbonyl electrophile	*n*	R^1	Yield (%)
$-(O-CH_2)_n-$ (as paraformaldehyde)	1.0	H	80 (4*S*,5*S*)-**IIIA**
$H_2N-CH_2-CH(OCH_3)_2$ (DMEA)[b]	1.0	CH_2-NH_2	65 (2*R*,4*S*,5*S*)-**IIIB**
O=CH-CH(OH)$_2$	0.5	R^2	33 (2*R*,4*S*,5*S*)-**IIIC**

[a]***p*-NitroPhenyl**; [b]2,2-**DiMethoxyEthylAmine**

Scheme 2. Previous examples for sulfuric transacetalization of *p*-nitrophenylserinol (1*S*,2*S*)-**IB**.

yielding condensates with acetone, followed by deprotection. Optically active acetonide (4*S*,5*S*)-**IIA** (Scheme 1, $R^1 = H$, $R^2 = R^3 = Me$) is a commercial and well-known chiral auxiliary.[10]

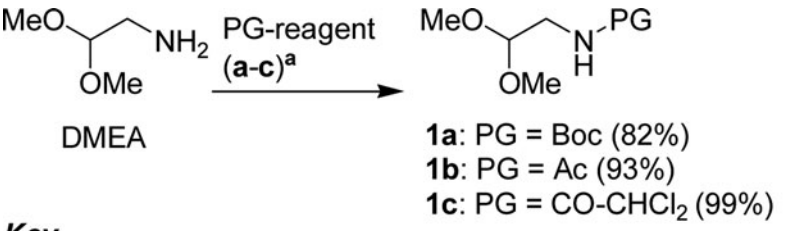
Based on our preceding expertise in the field of this sort of syntheses,[2,7] the aim of the present preliminary report consists of enlarging the number of masked carbonyl electrophiles in addition with those of *N*-protected forms of *p*-nitrophenylserinol (1*S*,2*S*)-**IB**, both envisaged as suitable partners for sulfuric transacetalization reaction. The feasibility of the latter in triplicate, providing a new family of optically active tripodands, was also investigated. A spotlight also concerned the use of phenylserinol **IA** in this purpose.

RESULTS AND DISCUSSION

Use of *p*-Nitrophenylserinol (1*S*,2*S*) IB in Sulfuric Transacetalization Conditions Providing Selectively *N*-Protected Derivatives of Diamino-1,3-dioxane (2*R*,4*S*,5*S*)-IIIB

Except for the previous use of the dimethylacetal of aminoacetaldehyde (2,2-dimethoxyethylamine, DMEA) in the synthesis of diamino-1,3-dioxane **IIIB**[7c,7d] (Scheme 2) and regardless of conditions for cycloacetalization of **IA**–**C**, so far all tested carbonyl electrophiles were actually either oxo- or formylated hydrocarbons, bearing no additional functional group (Scheme 1). Therefore, we primarily planned to *N*-protect DMEA to access additional masked carbonyl electrophiles, envisaged as well for sulfuric transacetalization, against arylserinols **IA** and **IB** (Scheme 3).

Compounds **1a** and **1b** were prepared with good or excellent yields in unsophisticated procedures already published by other authors.[11,12] In contrast, the *N*-dichloroacetyl derivative **1c** of DMEA was unknown up to now. Because crude amidoacetals **1a**–**c** displayed clean as convincing NMR and MS spectra, they were used as such in the next step of the syntheses.



Key

1a: 1 equiv. Boc_2O (**a**), 1 equiv. K_2CO_3, $CHCl_3$ / 0 °C → r.t. (12 h)
1b: 1 equiv. Ac_2O (**b**), 1 equiv. K_2CO_3, $CHCl_3$ / 0 °C → r.t. (12 h)
1c: 1 equiv. MeO-CO-$CHCl_2$ (**c**), 1 equiv. K_2CO_3, THF / reflux (15 h)

[a]PG: **P**rotecting **G**roup

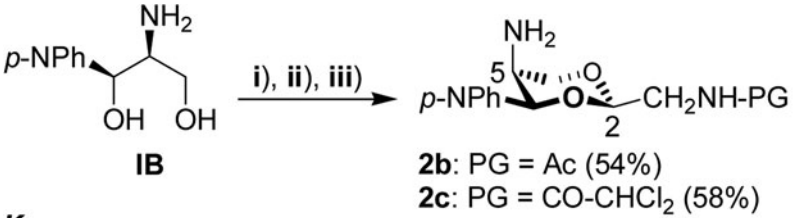
Scheme 3. Synthesis of DMEA *N*-protected derivatives.

With **1a**–**c** in our hands, we first submitted *p*-nitrophenylserinol (1*S*,2*S*)-**IB** to the title transacetalization protocol (Scheme 4).

We thus obtained the equatorially C-2 mono-*N*-protected forms **2b** and **2c** of the diamino-1,3-dioxane (2*R*,4*S*,5*S*)-**IIIB** with satisfactory yields; meanwhile, in the case of **1a**, decomposition of this *N*-Boc amidoacetal was observed. This failure motivated us to look for an alternative strategy to access a compound of type **2** based on Boc as PG (see later discussion). Decompositions of the reaction mixture also took place in the case of phenylserinol (1*S*,2*S*)-**IA** upon treatment with **1a**–**c**. That is, we kept in mind that Boc PG-group in **1a** and **IA** were inapt for this type of conditions.

To prepare regioisomers of **2b** and **2c**, bearing the NH-PG sequence in axial position C-5 of the 1,3-dioxane ring, we preliminarily *N*-(dichloro)acetylated (1*S*,2*S*)-**IB** and then successfully cyclized the resulting open-chain derivatives **3b** and **3c** in the previous conditions, in reaction with DMEA (Scheme 5).

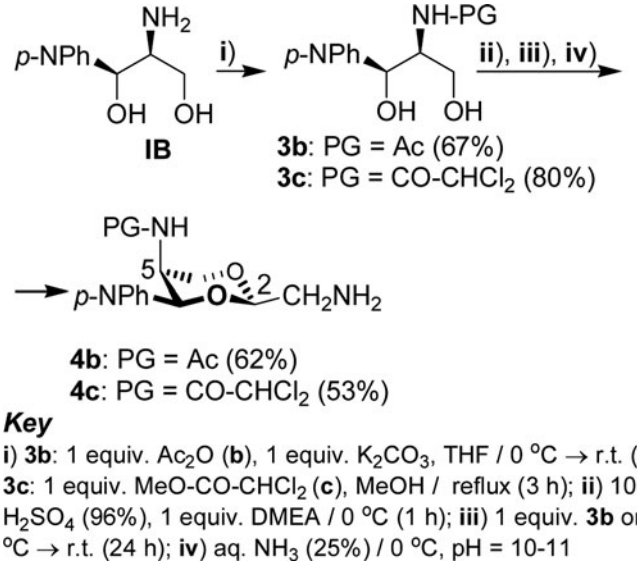
We mention the preparation of compound **3b** in optically active form (1*S*,2*S*)[13a] because, according to literature, only (*rac*)-**3b** was previously reported.[13b] The classic procedure[1,2] for *N*-dichloroacetylation of (1*R*,2*R*)-**IB** we applied in the case of its known (1*S*,2*S*) antipode in the synthesis of (1*S*,2*S*)-**3c**.



Key

i) 10 equiv. H_2SO_4 (96%) / 0 °C (1 h); **ii**) 1 equiv. **1b** or **1c** / 0 °C → r.t. (24 h); **iii**) aq. NH_3 (25%) / 0 °C, pH = 10-11

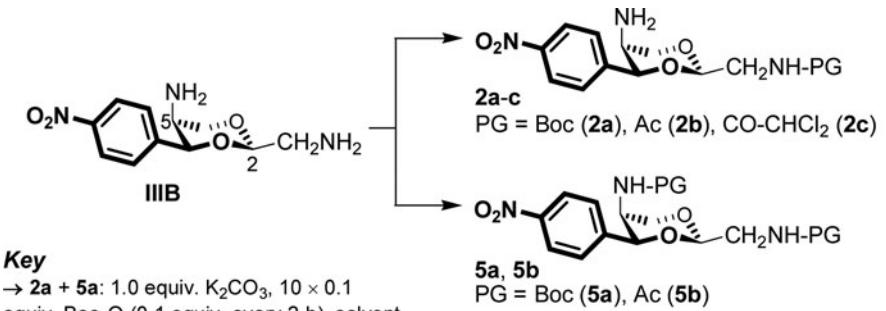
Scheme 4. Synthesis of equatorially *N*-protected forms of diamino-1,3-dioxane (2*R*,4*S*,5*S*)-**IIIB**.



Scheme 5. Synthesis of axially *N*-protected forms of diamino-1,3-dioxane (2*R*,4*S*,5*S*)-**IIIB**.

Selective *N*-Protection of Diamino-1,3-dioxane (2*R*,4*S*,5*S*)-IIIB

Because we were unable to obtain a compound of type **2** having Boc as PG (Scheme 4), in a second synthetic pathway, we decided to investigate the reactivity of the two differently located amino functionalities of (2*R*,4*S*,5*S*)-**IIIB** against all three PG-reagents (**a**–**c**) listed in Scheme 3 (Scheme 6).



Key

→ **2a** + **5a**: 1.0 equiv. K_2CO_3, 10 × 0.1 equiv. Boc_2O (0.1 equiv. every 2 h), solvent, 0 °C / r.t. (12 h)

→ **2b** + **5b**: 1.0 equiv. K_2CO_3, 10 × 0.1 equiv. Ac_2O (0.1 equiv. every 2 h), solvent, 0 °C / 0 °C (20 h)

→ **2c**: 10 × 0.1 equiv. MeO-CO-$CHCl_2$ (0.1 equiv. every 2 h), solvent, r.t / r.t. (12 h)

PG-Reagent	Solvent	Products (%)
Boc_2O (**a**)	$CHCl_3$	**2a** (45)[a], **5a** (20)[a]
	THF	**2a** (43), **5a** (22)
Ac_2O (**b**)	$CHCl_3$	**2b** (68), **5b** (16)
	THF	**2b** (60), **5b** (20)
Cl_2CH-CO-OMe (**c**)	$CHCl_3$	**2c** (57)[b]
	THF	**2c** (67)

[a]Partial conversions of **IIIB** into the depicted compounds as isolated amount of material after column chromatography
[b]Yield calculated based on the amount of material isolated after column chromatography

Scheme 6. Chemoselective mono-*N*-protection of diamino-1,3-dioxane (2*R*,4*S*,5*S*)-**IIIB**.

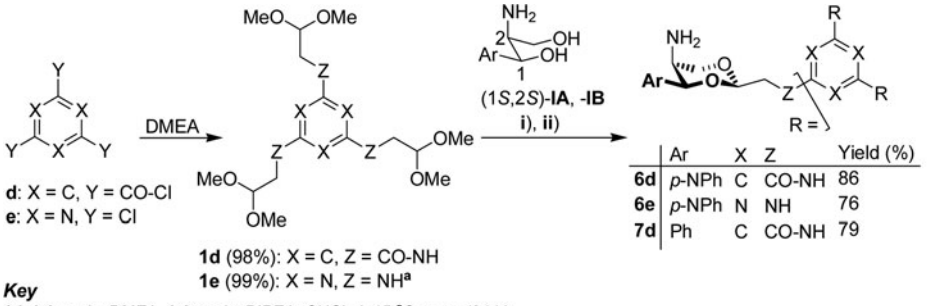
Thus, during the slow portionwise addition of Boc_2O (**a**) or Ac_2O (**b**) to **IIIB** in anhydrous $CHCl_3$ or THF, the thin-layer chromatographic (TLC) monitoring revealed the formation of two products. To our surprise, they were identified not as regioisomeric compounds but as mono-*N*-protected **2a, 2b** (major) against di-*N*-protected **5a, 5b** (minor) derivatives of **IIIB**. The total conversion of the PG-reagents (**a**) and (**b**) was nearly complete. In the case of the softest electrophile as PG-reagent (**c**), the *N*-protection was entirely regioselective, implying the sterically less congested aminomethyl group in equatorial position C-2 of **IIIb**. The quantitative results depicted in Scheme 6 could be subjected to some incipient comments:

i. Compounds **5a** and **5b** originated most probably from the equatorially *N*-protected precursors **2a** and **2b** because, in each case, no regioisomeric compounds **4a** or **4b** were detected. That is, **2a** and **2b** were more reactive than **IIIB** in reaction with PG-(**a**) and PG-(**b**), respectively.
ii. Chemoselectivity (%) as **2** > **5** was sensitive to no bulkiness (**a**) > (**b**) > (**c**) of the PG reagent, to be correlated with the sterically different location of the amino groups in **IIIB**. Chemoselectivity related satisfactorily with the decreasing electrophilicity of the PG reagents as **a** ~ **b** > **c**.
iii. For the PG reagents (**a**) and (**b**), chemoselectivity was slightly dependent on the solvent polarity, $CHCl_3$ ($\varepsilon = 4.81$) against THF ($\varepsilon = 7.52$), presumably because of the better solvating aptitude of the latter, favoring both the S_N2 polar transition states of amidations at C-2 as well as at C-5 1,3-dioxanic positions.

Sulfuric Transacetalization in Triplicate: Synthesis of New Tripodands, Feasibilities, and Failures

The feasibility of sulfuric transacetalization in duplicate was reported elsewhere[7c,7d] (compound **IIIC**, Scheme 2). Therefore, encouraged by these results, we decided to explore this methodology in triplicate (Scheme 7).

With this aim, we primarily prepared, in classical conditions, two *meta*-trivalent (het)aryl derivatives based on DMEA, the novel triple amide **1d** (starting from



Key

1d: 3.3 equiv. DMEA, 3.3 equiv. DIPEA, $CHCl_3$ / -15 °C → r.t. (24 h)
1e: 3.0 equiv. DMEA, 3.0 equiv. K_2CO_3, 1,4-dioxane / r.t. (12 h) / reflux (35 h)[a]
6e: **i)** 3.0 equiv. **IB**, 30.0 equiv. H_2SO_4 (96%) / 0 °C → r.t. (24 h); **ii)** aq. NH_3 (25%) / 0 °C, pH = 10-11
6d, **7d**: **i)** 3.0 equiv. **IA** or **IB**, 3.0 equiv. H_2SO_4 (96%), 45.0 equiv. TFA[b] / 0 °C → r.t. (24 h); **ii)** aq. NH_3 (25%) / 0 °C, pH = 10-11
[a]Our conditions and yield (lit., Ref. 14: 80.8% yield); for the characterisation of this compound see Supplementary Material section
[b]TFA: trifluoroacetic acid

Scheme 7. Sulfuric transacetalization in triplicate producing tripodands **6d, 6e,** and **7d**.

trimesic acid trichloride **d**) and the known melamine **1e**[14] (starting from cyanuric chloride **e**). Both *N*-functionalizations of DMEA gave excellent yields. Then, we tested cycloacetalization of *p*-nitrophenylserinol **IB** upon treatment with **1d** and **1e**. We thus accessed the equatorially anchored trimers **6d** and **6e** respectively with good results. However, as one can see, the "typical" sulfuric transacetalization procedure used so far (10 equiv. H_2SO_4 : 1 equiv. **IB**) worked properly in the case of the synthesis of dioxanic-melamine **6e** only. In the same conditions, the reaction between trisamide **1d** and **IB** gave a complex as decomposed reaction mixture. Therefore, we considered, in this latter case, a moderation of the acidity strength of the medium by reducing the molar ratio H_2SO_4:**IB** from 10:1 to 1:1 and replacing the excess of concentrated H_2SO_4 by trifluoroacetic acid, i.e., 15 equiv. TFA : 1 equiv. **IB**. Our option was fruitful, though limited to the reaction between **1d** and **IB** (→**6d**) then **1d** and **IA** (→**7d**). In spite of this modification, cycloacetalization involving **1e** + **IA** failed to afford the corresponding trimer whose formation was just detected by MS in a multicomponent raw material.

Compounds **6d, 6e,** and **7d** can also be seen as the first tripodands[15] built on arylserinol-based amino-1,3-dioxane skeleton. Except for DMF and DMSO, they manifested low solubility in other organic solvents. Fortunately, their purification could be accomplished simply by (i) acid-base treatment and (ii) crystallization from boiling ethanol. All compounds **1d, 1e, 6d, 6e,** and **7d** provided convincing analytical and spectral data. As expected, on the ^{1}H NMR timescale at room temperature in DMSO-d_6, melamines **1e** and **6e** and trisamides **6d** and **7d** exhibited blocked orientations of their acetalic arms due to the well-known restricted rotation about the partial double bonds C(*s*-triazine)-NH (exocyclic)[7d,16] and $>C(=O)\text{-}NH\text{-} \leftrightarrow > C(\text{-}O^-) = NH^+\text{-}$.[17–19]

CONCLUSIONS

In summary, we extended the sulfuric transacetalization methodology directed to a selectively *N*-protected (1*S*,2*S*)-*p*-nitrophenylserinol-based (2*R*,4*S*,5*S*)-5-amino-2-aminomethyl-1,3-dioxane by (i) using two masked carbonyl electrophiles, as *N*-protected forms of the dimethylacetal of aminoacetaldehyde in reaction with *p*-nitrophenylserinol, and (ii) by using two *N*-protected derivatives of *p*-nitrophenylserinol in reaction with the dimethylacetal of aminoacetaldehyde. The title diamino-1,3-dioxane can be also regioselectively *N*-protected with respect to the equatorial aminomethyl group upon treatment with typical protecting group reagents. Selectivity correlates rather with the electrophilicity strength of the protecting group reagent than with its bulkiness or the solvent solvation capacity. Submission to (moderated) sulfuric transacetalization conditions of two *meta*-trivalent (het)aryl derivatives based on DMEA in reaction with (1*S*,2*S*)-arylserinols afforded the first series of tripondands built on arylserinolic amino-1,3-dioxane skeleton. Their potential use in iterative synthesis as new *meta*-trivalent dendritic cores will be reported in the near future.

EXPERIMENTAL

Melting points were measured on an Electrothermal instrument. NMR spectra were recorded on Bruker AV 400, AV 500, or AV 600 instruments operating at 400,

500, or 600 MHz for ^{1}H and at 100, 125, or 150 MHz for ^{13}C nuclei respectively. All chemical shifts (δ values) are given in parts per million (ppm); all homocoupling patterns ($^{n}J_{H,H}$ values) are given in hertz. TLC was performed by using aluminium sheets with silica gel 60 F_{254} (Merck); column chromatography was conducted on silica gel 60 (40–63 μm, Merck). IR spectra were recorded on a Bruker FT-IR Vector 22 spectrometer. Microanalyses were performed on a Carlo Erba CHNOS 1160 apparatus. Mass spectra were carried out on a LTQ ORBITRAP XL (Thermo Scientific) instrument, which was externally calibrated using the manufacturer's ESI(+) calibration mix. The samples were introduced into the spectrometer by direct infusion. Specific rotations $[\alpha]_D^T$ were measured on a Polamat Karl-Zeiss Jena instrument. All reagents and solvents were of commercial quality and used as such with no supplementary purification except for methyl dichloroacetate, which was freshly distilled prior to use. The starting (1*S*,2*S*)-2-amino-1-phenylpropane-1,3-diol (1*S*,2*S*)-**IA** (phenylserinol, CAS No. 28143-91-1) had 99% enantiomeric purity, $[\alpha]_D^{20} + 25.7$ (*c* 1, MeOH). The starting (1*S*,2*S*)-2-amino-1-(4-nitrophenyl)propane-1,3-diol (1*S*,2*S*)-**IB** (*p*-nitrophenylserinol, CAS No. 2964-48-9) has a 99% enantiomeric purity as $[\alpha]_D^{25} + 31.0$ (*c* 1, HCl 6 M). Synthesis and data of compound (2*R*,4*S*,5*S*)-**IIIB**, $[\alpha]_D^{25} + 146.2$ (*c* 0.5, DMSO), we reported elsewhere.[7c,7d] Hereafter, *p*-NPh stands for the *p*-nitrophenyl group. Compound **1e** was previously reported;[14] however, its complete structural characterization as well as its improved synthesis are described in this work.

Typical Procedure for Preparation of Compounds 2b and 2c by Sulfuric Transacetalization of *p*-Nitrophenylserinol (1*S*,2*S*)-IB: Preparation of Compound 2c

At 0 °C and with vigorous stirring, fine powdered *p*-nitrophenylserinol (1*S*,2*S*)-**IB** (1.00 g, 4.72 mmol) was slowly added to concentrated H_2SO_4 (96%, 2.62 mL, 4.82 g, 47.20 mmol). The resulted slurry was stirred at 0 °C for 1 h, and then crude *N*-dichloroacetyl-2,2-dimethoxyethylamine **1c** (1.02 g, 4.72 mmol) was rapidly injected at this temperature. The reaction mixture was allowed to reach room temperature and kept as such with vigorous stirring for an additional 24 h. After this period, TLC monitoring (eluent EtOH/CH_2Cl_2 3:1 v/v, visualization in UV at $\lambda = 254$ nm) indicated the complete consumption of **IB**. At 0 °C, the reaction mixture was carefully poured into $CHCl_3$ (100 mL) and aqueous ammonia (25%, 20.00 mL, 19.60 g, 288.00 mmol) was diluted 1:1 g/g with ice. The resulting pH was 10–11 and the organic layer was recovered. The aqueous layer was extracted with $CHCl_3$ (2 × 25 mL). The combined $CHCl_3$ solution was washed with water (25 mL), dried over anhydrous Na_2SO_4, and then evaporated in vacuum to dryness to yield 1.27 g crude product **2c** as brownish oil. This was purified by column chromatography on silica gel (eluent EtOH/CH_2Cl_2 3:1 v/v) to give 0.9 compound **2c** (58% yield with respect to **IB**) as an yellow solid.

(2*R*,4*S*,5*S*)-5-Amino-2-(*N*-dichloroacetyl)aminomethyl-4-(4-nitrophenyl)-1,3-dioxane 2c

Yellow solid; mp 62–64 °C. R_f(75% EtOH/CH_2Cl_2) = 0.60. Anal. calcd. for $C_{13}H_{15}Cl_2N_3O_5$: C, 42.87; H, 4.15; N, 11.54. Found: C, 43.08; H, 3.99; N, 11.28.

IR (KBr) ν_{max} 3366, 2861, 1715, 1700, 1520, 1349, 1150, 1110, 1013, 878, 812, 742, 707 cm^{-1}. ^1H and 2D-^1H, ^1H-COSY NMR (400 MHz, $CDCl_3$) δ_H 1.47 (br s, 2H, NH_2), 2.97 (s, 1H, H-5-e), 3.65 (dd, *J* 6.1, 3.8 Hz, 1H, CH_2-NH) and 3.68 (dd, *J* 6.1, 4.4 Hz, 1H, CH_2-NH), 4.14 (dd, *J* 11.9, 1.8 Hz, 1H, H-6-a), 4.18 (dd, *J* 11.9, 2.0 Hz, 1H, H-6-e), 4.95 (dd app. t, *J* 4.0 Hz, 1H, H-2-a), 5.04 (s, 1H, H-4-a), 5.99 (s, 1H, $CHCl_2$), 6.97 (br s, 1H, NH), 7.47 (d, *J* 8.6 Hz, 2H, H-2, -6, *p*-NPh), 8.24 (d, *J* 8.6 Hz, 2H, H-3, -5, *p*-NPh) ppm. ^{13}C NMR-J_{mod} (100 MHz, $CDCl_3$) δ_C 43.2 (CH_2-NH), 49.6 (C-5), 66.5 ($CHCl_2$), 72.8 (C-6), 80.2 (C-4), 99.0 (C-2), 123.9 (C-2, -6, *p*-NPh), 126.5 (C-3, -5, *p*-NPh), 145.9 (C-1, *p*-NPh), 147.5 (C-4, *p*-NPh), 164.6 (C=O) ppm. HRMS-APCI *m/z* (relative intensity): 364.0446 (100) $[M+H]^+$. $[M+H]^+$ calcd. for $C_{13}H_{16}Cl_2N_3O_5$, 364.0469. $[\alpha]_D^{25} + 170.6$ (*c* 0.5, DMSO).

Typical Procedure for Regioselective *N*-Protection of Diamino-1,3-dioxane (2*R*,4*S*,5*S*)-IIIB: Preparation of Compounds 2b and 5b

Anhydrous K_2CO_3 (0.54 g, 3.95 mmol) was added to a solution obtained by dissolving diamino-1,3-dioxane (2*R*,4*S*,5*S*)-**IIIB** (1.00 g, 3.95 mmol) in anhydrous $CHCl_3$ (10 mL), and the resulted suspension was cooled at 0 °C with vigorous stirring. At this temperature, acetic anhydride (0.37 mL, 0.40 g, 3.95 mmol) was added as 10 equal portions every 2 h. After this period, TLC monitoring (eluent EtOH/CH_2Cl_2 3.5:1 v/v visualization in UV at $\lambda = 254$ nm) indicated formation of two products, **2b** and **5b,** and the presence of the starting material **IIIB**. Stirring was continued for additional 20 h at 0 °C, then minerals were filtered off, and the product was well washed with anhydrous $CHCl_3$. The organic filtrate was evaporated in vacuum to give 1.20 g crude material. This was separated by column chromatography on silica gel (eluent EtOH/CH_2Cl_2 3.5:1 v/v) to provide, in order, compound **5b** (0.21 g, 16% partial conversion of **IIIB**) and then compound **2b** (0.79 g, 68% partial conversion of **IIIB**).

Typical Procedure for Preparation of Compounds 6d, 6e, and 7d: Preparation of Compound 6d

Fine powdered *p*-nitrophenylserinol (1*S*,2*S*)-**IB** (1.35 g, 6.36 mmol) was added portionwise and with vigorous stirring to cooled trifluoroacetic acid (7.40 mL, 10.88 g, 95.44 mmol) in such a rhythm that temperature did not rise up to 0 °C. After additional 2 h of stirring at 0 °C, to the resulted fine suspension H_2SO_4 concentrate (96%, 0.35 mL, 0.65 g, 6.36 mmol) was injected dropwise at the same temperature. Fine powdered compound **1d** (1.00 g, 2.12 mmol) was then added portionwise at 0 °C and the reaction mixture was let to reach the room temperature and was kept stirring for 24 h (TLC monitoring, eluent EtOH/NH_3 25% aqueous 4:0.1 v/v, visualization in UV at $\lambda = 254$ nm, one major spot). At 0 °C and with vigorous stirring, the reaction mixture was carefully poured in aqueous ammonia (25%, 15.20 mL, 3.46 g, 203.60 mmol) diluted with water (20 mL) and ice (20 g). The basic suspension (pH = 10–11) was filtered off and the solid was well washed to neutrality with cooled water. After drying, 1.80 g crude product **6d** was obtained. This was taken with aqueous 10% HCl (20 mL). The resulting fine brownish suspension (pH 0.5–1.0) was filtered off with charcoal and the filtrate was made alkaline (pH = 10–11) with anhydrous K_2CO_3 when

6d precipitated. After filtering, washing to neutrality with water, and drying, 1.75 g of compound **6d** was obtained. This material was finally taken with boiling EtOH (18 mL) to give, after crystallization, 1.67 g pure compound **6a** (86% yield with respect to **1d**).

1,3,5-Tris{*N*-{[(2*R*,4*S*,5*S*)-5-amino-4-(4-nitrophenyl)-1,3-dioxan-2-yl] methyl}aminocarbonyl}benzene 6d

Yellow solid; mp 182–184 °C (dec.). R_f(97.5% EtOH/NH_3 25% aq.) = 0.37. Anal. calcd. for $C_{42}H_{45}N_9O_{15}$: C, 55.08; H, 4.95; N, 13.76. Found: C, 55.11; H, 4.75; N, 13.88. IR (KBr) ν_{max} 3400, 3074, 2869, 1658, 1518, 1348, 1285, 1150, 1105, 1007, 860, 783, 742 cm^{-1}. ^1H and 2D-^1H,^1H-COSY NMR (600 MHz, DMSO-d_6, 298 K) δ_H 2.95 (br s, 3H, H-5-e), 3.57 (br s, 12H, CH_2NH, NH_2), 3.95 (br d, *J* 9.9 Hz, 3H, H-6-a), 4.08 (br d, *J* 9.9 Hz, 3H, H-6-e), 4.99 (br s, 3H, H-2-a), 5.13 (br s, 3H, H-4-a), 7.61 (br d, *J* 7.5 Hz, 6H, H-2, -6, *p*-NPh), 8.21 (br d, *J* 7.5 Hz, 6H, H-3, -5, *p*-NPh), 8.46 (br s, 3H, H-2, -4, -6, benzene), 8.92 (br s, 3H, NH) ppm; ^1H and 2D-^1H,^1H-COSY NMR (400 MHz, DMSO-d_6, 353 K) δ_H 3.00 (br s, 3H, H-5-e; 6H, NH_2), 3.61 (br s, 6H, CH_2NH), 3.98 (br d, *J* 11.2 Hz, 3H, H-6-a), 4.11 (br d, *J* 11.2 Hz, 3H, H-6-e), 5.03 (br s, 3H, H-2-a), 5.12 (br s, 3H, H-4-a), 7.63 (br d, *J* 7.6 Hz, 6H, H-2, -6, *p*-NPh), 8.19 (br d, *J* 7.5 Hz, 6H, H-3, -5, *p*-NPh), 8.44 (br s, 3H, H-2, -4, -6, benzene), 8.58 (br d, *J* 4.8 Hz, 3H, NH) ppm. ^{13}C NMR J_{mod} (150 MHz, DMSO-d_6, 298 K) δ_C 43.2 (CH_2NH_2), 48.8 (C-5), 72.6 (C-6), 79.2 (C-4), 99.1 (C-2), 123.1 (C-2, -6, *p*-NPh), 127.0 (C-3, -5, *p*-NPh), 129.0 (C-2, -4, -6, benzene), 134.7 (C-1, -3, -5, benzene), 146.6 (C-1, *p*-NPh), 147.6 (C-4, *p*-NPh), 165.9 (C=O) ppm. HRMS-ESI(+) (relative intensity) *m*/*z*: 916.3060 (100) $[M+H]^+$. $[M+H]^+$ calcd. for $C_{42}H_{46}N_9O_{15}$, 916.3113. $[\alpha]_D^{25}$ + 121.0 (*c* 0.5, DMSO).

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SUPPORTING INFORMATION

(Typical) procedures for preparations of compounds **1a, 1b, 1c, 3b, 4b, 4c, 1d,** and **1e**; full analytical data of compounds **1a, 1b, 1c, 2b, 3b, 4b, 4c, 2a, 5a, 5b, 1d, 1e, 6e**, and **7d**; ^1H and ^{13}C NMR spectra of compounds **1a, 1b, 1c, 2b, 4b, 4c, 3b, 2a, 5a, 5b, 1d, 1e, 6d, 6e**, and **7d**; and MS of compounds **6d, 6e,** and **7d** for this article can be accessed on the publisher's website.

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