

Orthoamides and Iminium Salts, LXXX [1]. C-Glycosyl Alkynecarboxylic Acid Orthoamides. Versatile Intermediates in the Synthesis of New Types of Highly Substituted C-Nucleoside Analogs

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Dedicated to Professor Christian Vogel on the occasion of his 60th birthday

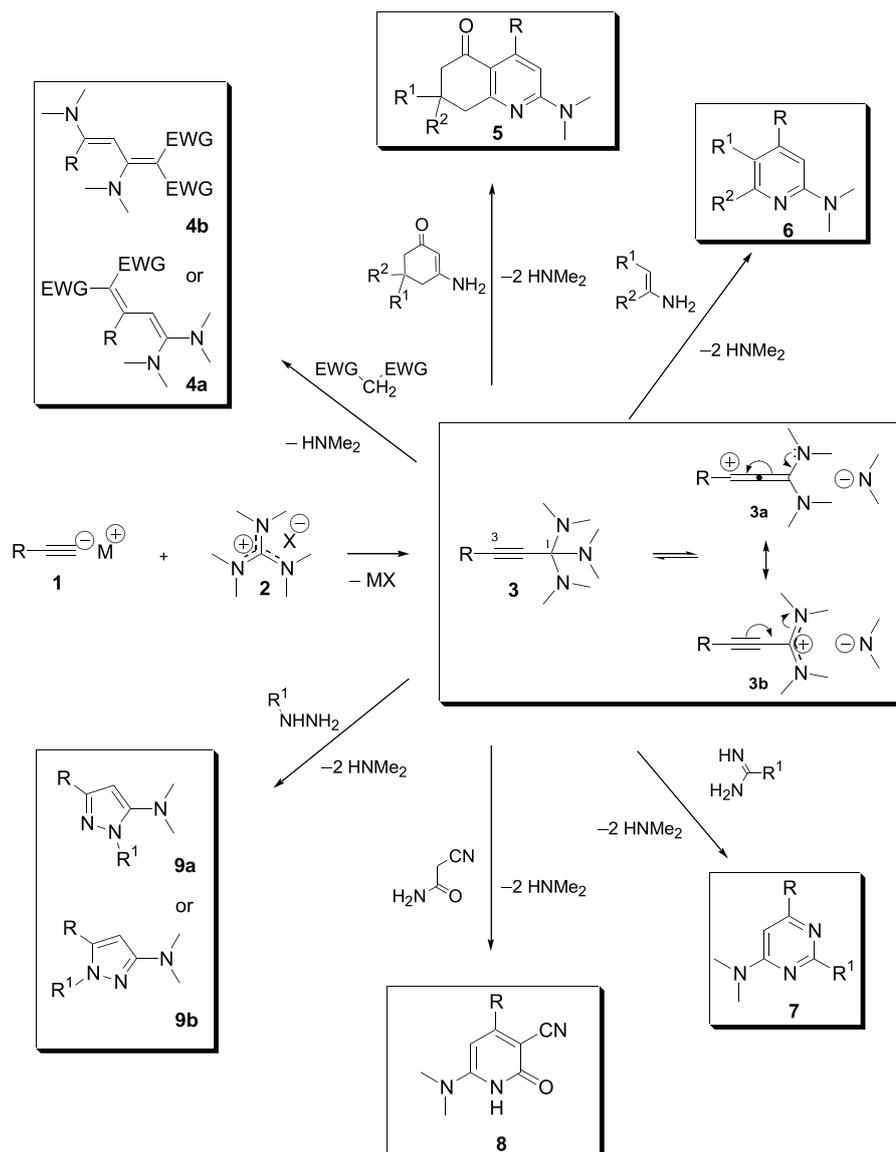
The C-glycosyl alkynecarboxylic acid orthoamides **22** and **23** are proposed as versatile precursors for the synthesis of new types of C-nucleoside analogs. The new synthetic strategy includes alkynylation of protected aldoses **13** or ketoses by Grignard ethynylation or Barbier propargylation, O-protection of the resulting alkynols **14–16**, and nucleophilic addition of the metalated protected terminal alkynes **20** and **21** to peralkylguanidinium salt **2** to afford the corresponding alkynecarboxylic acid orthoamides **22** and **23**, which in reactions with mono or bis-nucleophiles could serve as building blocks for the construction of a wide variety of C-nucleoside-like binary conjugates. All the steps are demonstrated on 2,4,3,5-bis(4-methoxybenzylidene)-protected L-xylose **11** as a model compound. The synthesis of a representative series of C-glycosidic conjugates of highly substituted “push-pull” 1,3-butadienes **32–35**, pyrimidines **24–31**, and 2-pyridones **36–39** is included. The stereochemistry of all described compounds is established by 2D-NMR techniques. A general character of the proposed synthetic strategy, when applied to different appropriately protected sugar derivatives, is suggested, and a biomedical applicability of the described type of conjugates is expected.

Key words: *N,N,N',N',N'',N''*-Hexamethylguanidinium Chloride, Alkynecarboxylic Acid Orthoamides, O-Protected Aldose, Ethynylation, Propargylation, Stereochemical Assignment, C-Nucleosides

Introduction

The antibacterial, antiviral and cytostatic activities observed in a number of naturally occurring C-nucleosides triggered considerable interest in the design, synthesis and biological evaluation of new C-nucleoside analogs. Thus, the combinatorial C–C bond fusion of natural or chemically modified, cyclic or open-chain sugar moieties to diverse biomedically interesting aglycones has become a valuable source of new, C-nucleoside-like derivatives that are potentially applicable in therapy. In this regard, new synthetic strategies for the construction of a C-nucleoside type of binary conjugates are continuously well appreciated [2–16].

Previous studies highlighted alkynecarboxylic acid orthoamides **3** (Scheme 1) as very useful reagents in organic synthesis. They are readily accessible by nucleophilic addition of metalated terminal alkynes **1** to peralkylated guanidinium salts **2** (Scheme 1) [17–21]. Alkynecarboxylic acid orthoamides **3** behave as electrophilic reagents, equivalent to the corresponding resonance-stabilized propiolamidinium species **3b**. Due to delocalization of the positive charge, both C(1) and/or C(3) atoms in the resonance forms **3a** ↔ **3b** can be involved in reactions with mono- and bis-nucleophiles. These chemical features of the alkynecarboxylic acid orthoamides have been already utilized in the synthesis of a variety of “push-pull” 1,3-butadienes **4a** and **4b**, and in reactions with CH₂



Scheme 1. Diversity of some previously described condensation products from alkynecarboxylic acid orthoamides **3** [17–21] (EWG = electron withdrawing group).

acids and various heterocyclic compounds. Thus, orthoamides **3** reacted with enamines to form pyridines **5** and **6**, with amidines to pyrimidines **7**, with cyanoacetamide to 2-pyridones **8**, with hydrazines to pyrazoles **9**, *etc.* [17–21].

The fact that terminal alkyne derivatives of sugars are easily available by direct Grignard ethynylation [2–16, 22–29] or Barbier propargyla-

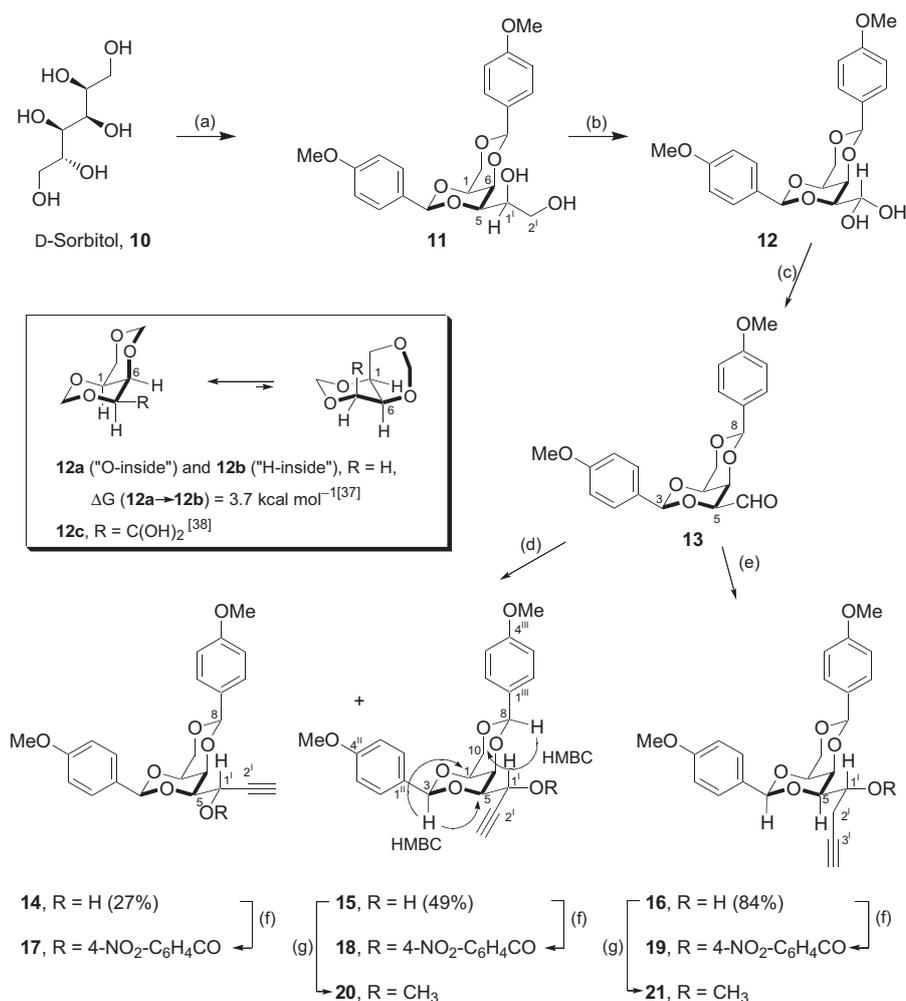
tion [30–32] of protected aldoses or ketoses led to the idea that sugar-derived alkynecarboxylic acid orthoamides **3** (Scheme 1), where R is a protected sugar residue, could serve as potentially convenient precursors in the synthesis of new types of C-nucleoside-like conjugates with literally unexplored biological activity (similar to the types of derivatives highlighted in Scheme 1, where R is a sugar residue). A previous

study illustrating this approach on one protected ketose example was encouraging [33]. Herein we describe the results of our efforts to expand this methodology to protected aldoses.

Results and Discussion

Earlier reports have emphasized the antiviral activity of some benzylidene-protected aldopentoses and their derivatives [34, 35], which motivated us to choose

the 4-methoxybenzylidene protected L-xylose **13** as the starting material for the present study. Compound **13** was prepared by a published reaction sequence [36] (Scheme 2). A practical improvement was achieved in the first step where the acetalization of D-sorbitol (**10**) was performed more conveniently in acetic acid as catalyst and reaction medium, from which the desired 4-methoxybenzylidene-protected compound **11** separates in practically pure state and higher yield. The periodate oxidation of the vicinal diol **11** led to the



Scheme 2. Synthesis of 4-MeO-benzylidene-protected L-xylose **13** and its alkynylated derivatives **14–16**. Some of the H atoms are omitted for clarity. *Reagents and conditions*: (a) 4-MeO-benzaldehyde, acetic acid, r. t., 48 h, 56%; (b) NaIO₄, 80% aq. dioxane, r. t. 48 h, quant.; (c) toluene reflux with a Dean-Stark trap, 86%; (d) ethynylmagnesium chloride, THF, r. t., 2.5 h; (e) propargyl bromide, Zn dust, DMF-diethyl ether, 35 °C to r. t., 84%; (f) 4-nitrobenzoyl chloride, TEA, MeCN, r. t. overnight, 72%; (g) NaH, DMF, MeI, r. t., 3 h, 94%. The long-range heteronuclear correlation (2D HMBC) between C(3)H, C(1) and C(5) and between C(8)H and C(10) atoms is illustrated on the structure of compound **15**.

aldehyde hydrate **12**, which according to [36] was dehydrated by azeotropic distillation with toluene to the desired protected aldopentose **13**.

The reaction of aldehyde **13** with ethynylmagnesium chloride was almost quantitative, but showed poor diastereoselectivity and led to a mixture of two epimeric alkynols **14** and **15** in *ca.* 1 : 1.8 ratio (Scheme 2). Fortunately, we succeeded in the convenient large-scale separation of this mixture by simple recrystallization from methanol where the ¹S-epimer **14** (27% isol.) crystallized almost quantitatively. The major ¹R-epimer **15** was isolated from the mother liquor in 49% yield and used further in our study.

Additionally, with propargyl bromide and activated Zn dust in DMF-diethyl ether (1 : 1) mixture, analogously to a described procedure [30–32], the 4-methoxybenzylidene-protected L-xylose **13** was converted to the homoalkynol **16** in 84% yield. The reaction showed excellent diastereoselectivity, and the ¹R-epimer was practically the sole product.

Stereochemical assignment

Similar to *cis*-decalin, the unsubstituted *cis*-2,4,7,9-tetraoxabicyclo[4.4.0]decane is expected to undergo conformational ring flip around the C(1)–C(6) bond giving rise to a mixture of two conformers (**12a** and **12b**, R = H, Scheme 2, highlighted in rectangle). Earlier studies demonstrated that the “O-inside” conformer **12a** (R = H) is thermodynamically favored [37]. An equatorial substitution at C(5) in **12a** (R ≠ H) would restrict additionally the ring inversion **12a**→**12b** due to steric repulsion between the axial substituents in **12b** (R ≠ H). All compounds in the present study are 3,5,8-trisubstituted *cis*-2,4,7,9-tetraoxabicyclo[4.4.0]decane derivatives. Thus, the “O-inside” structures with axial C(1)H and C(5)H and equatorial C(6)H are preferred. The crystal structure of the closely related compound **12c** (Scheme 2, highlighted in rectangle) has been described and confirms such a molecular arrangement [38].

In order to determine the absolute configuration of the newly formed stereogenic center at C(1¹) in the epimeric alkynols **14**, **15**, and **16**, their 4-nitrobenzoyl derivatives **17**, **18** and **19** were prepared (Scheme 2 and Fig. 1). The entirely reverse magnetic anisotropy characteristics in the close proximity over the aromatic 4-nitrobenzoyl (shielding) and around the ethynyl (deshielding) [39] groups and

their inverted orientation in both epimeric derivatives **17** and **18** and the homologous **19** were expected to alter the chemical shifts of the eclipsed protons in a predictable manner. The long-range heteronuclear correlations (2D HMBC) between C(3)H, C(1) and C(5) and between C(8)H and C(10) atoms (shown in Scheme 2), which were observed in all here reported 5-substituted 3,8-bis(4-methoxyphenyl)-*cis*-2,4,7,9-tetraoxabicyclo[4.4.0]decane derivatives, were particularly useful key spectral features for the identification of the ¹H and ¹³C NMR signals of the studied compounds. In the ¹H NMR spectra of all three compounds **17**, **18** and **19**, the C(3)H signals are shifted downfield compared with the C(8)H signals.

The ¹H NMR spectra of compounds **17**, **18** and **19** show a C(5)H–C(1¹)H vicinal coupling constant (³J_{H,H}) of 8.8 Hz for **17** and **18**, and 8.5 Hz for **19**, which strongly indicates that in solution the almost antiperiplanar orientation of these protons in each of these compounds is favored. In such an arrangement the 4-nitrobenzoyl and the ethynyl substituents at C(1¹) would diverge around the C(5)–C(1¹) bond axis eclipsing the benzylidene groups at C(3) and C(8). In the ¹R-epimer **18** the 4-nitrobenzoyl group (shielding) would be situated over C(8)H and the ethynyl group (deshielding) over C(3)H, which would cause divergence of the chemical shifts of these signals whereas in the ¹S-epimer **17** the 4-nitrobenzoyl group eclipsing C(3)H and ethynyl group eclipsing C(8)H should cause their convergence.

Fig. 1 shows fragments of the ¹H NMR spectra of compounds **17**, **18** and **19**, including the most indicative benzylidene C(3)H, C(8)H and C(1¹)H signals. The C(3)H (δ = 5.80 ppm) and C(8)H (5.50 ppm) signals of the 4-nitrobenzoyl derivative **18** are significantly divergent (Fig. 1b) compared to the analogous signals of its epimeric compound **17** (Fig. 1a). Thus, compound **18** and its precursor **15** could be assigned the ¹R-configuration.

The significant upfield shift of the C(8)H signal (at 5.51 ppm) of compound **19** and the large divergence between C(3)H and C(8)H signals (Fig. 1c) resemble the spectral features of compound **18** and are consistent with a 4-nitrobenzoyl moiety eclipsing the C(8) benzylidene group, which suggests that compound **19** has the same configuration at C(1¹) as compound **18** and together with its precursor **16** also has ¹R configuration. The presence of a methylene linker at C(1¹) in compound **19** alters the spacial orientation

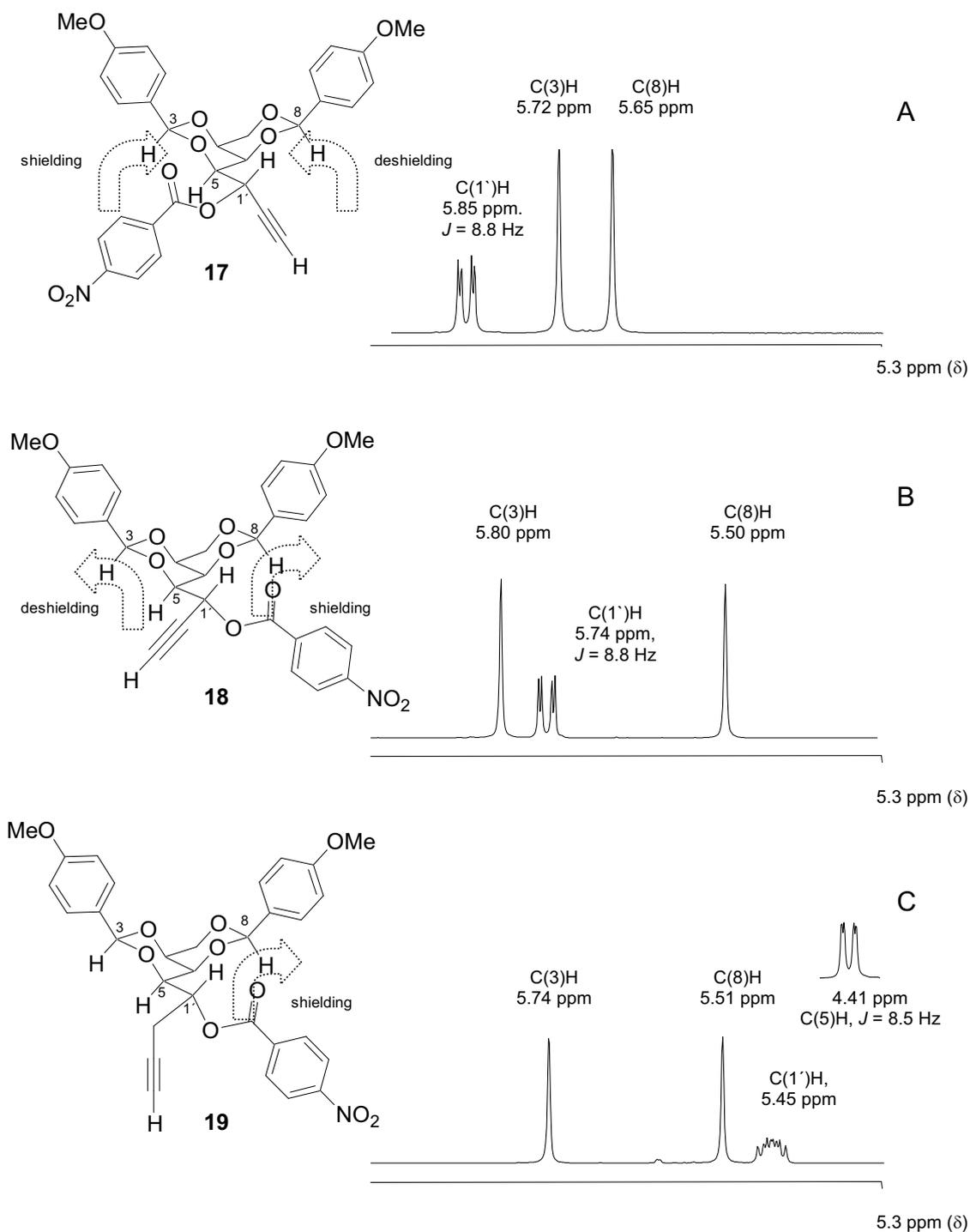


Fig. 1. Stereochemical assignment of the 4-nitrobenzoyl derivatives **17**, **18** and **19** based on the specific through-space influence of the 4-nitrobenzoyl (shielding) and ethynyl (deshielding) groups on the ^1H NMR chemical shift of the eclipsed protons at C(3) and C(8). Some of the H atoms are omitted for clarity.

of the alkyne group, which questions the degree of its through-space influence on the C(3)H chemical shift.

Synthesis of the C-nucleoside analogs

Our preliminary attempts to use a trimethylsilyl-protected derivative of compound **15** (Scheme 2, where R is SiMe₃) as starting material for the orthoamide preparation failed due to the instability of the protective group under the reaction conditions. Therefore the alkynols **15** and **16** were protected by *O*-methylation, and the corresponding I¹-OMe derivatives **20** and **21** were used as starting material in the preparation of the orthoamides **22** and **23** (Scheme 3).

Under strictly anhydrous conditions in THF under N₂ atmosphere the *in situ*-lithiated compounds **20** and **21** were introduced into the reactions with freshly dried (110 °C, 0.1 Torr, 2 h) hexamethylguanidinium chloride (**2**), carried out for 7 days at r.t., similar to a previously reported procedure [17–21] (Scheme 3). The water sensitivity of the alkynecarboxylic acid orthoamides reduces the choice of isolation methods to distillation or occasionally crystallization. Extraction or chromatographic methods are inapplicable [17–21]. Unfortunately, our attempts to isolate the orthoamides **22** and **23** (Scheme 3) by crystallization were unsuccessful. Therefore we used the *in situ* prepared solutions of these compounds for further transformations.

The reactions of orthoamides **22** and **23** with 1,3-bisnucleophiles of the type RC(=NH)NH₂ (amidines and guanidines) in THF at 65 °C (external) for 3 h led to smooth heterocyclization yielding the corresponding 6-dimethylamino-pyrimidine derivatives **24–31** in fair to good yields.

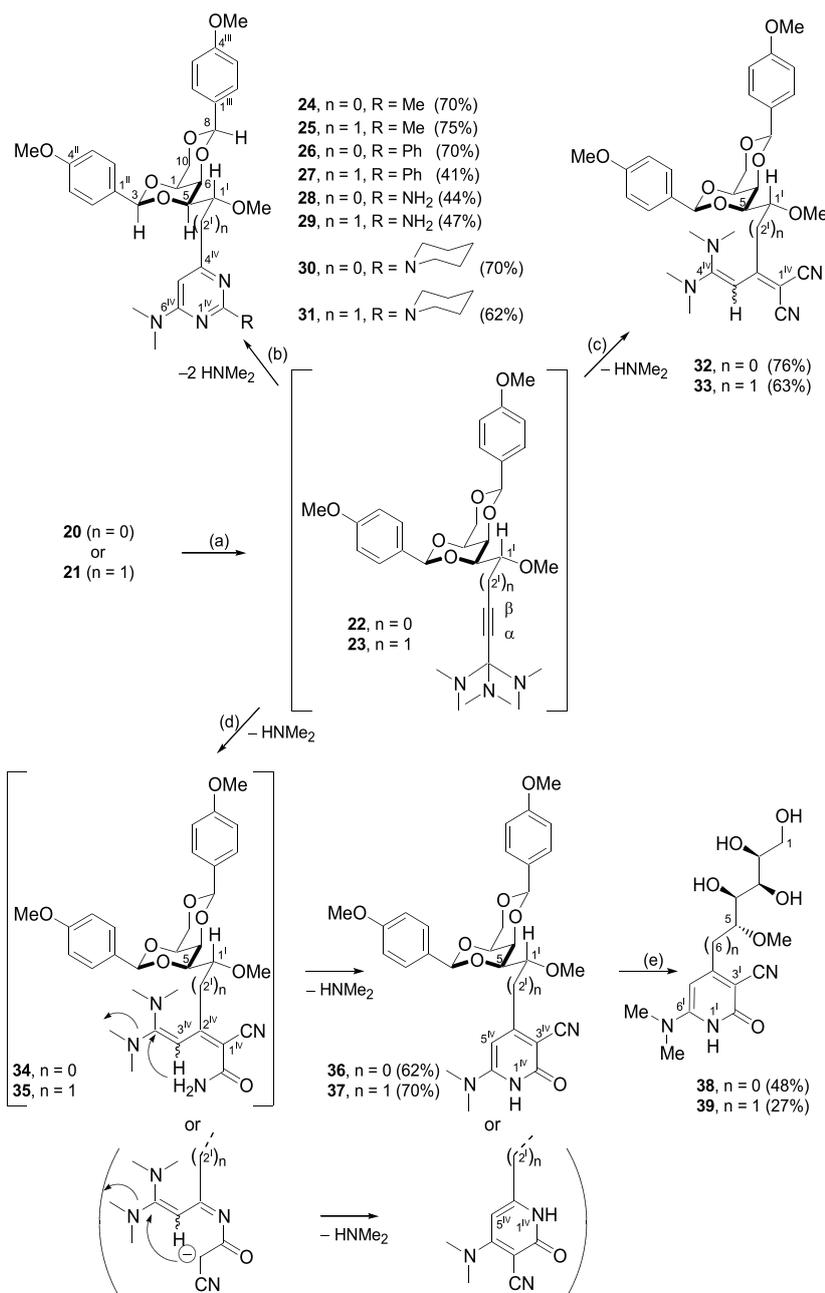
The reactions of orthoamides **22** and **23** with malonitrile in THF for 24 h at r.t. yielded the intensely yellow-orange ketene amins **32** and **33** in good yields.

In the ambient-temperature (297 K) ¹H NMR spectrum of compound **32**, with a ketene amina functionality directly attached to C(1^I), the two NMe₂ groups appear as a singlet at δ = 2.90 ppm and both display long range correlations (2D HMBC) with carbon atom C(4^{IV}). Additionally, there is evidence for long range correlations between C(1^I)H and the butadiene quaternary C(1^{IV}) and between C(3^{IV})H and C(1^{IV}). These spectral data indicate that the nucleophilic attack of the malonitrile takes place on the β-C atom of the or-

thoamide **22** with the exclusive formation of the ketene amina **32** (similar to **4a** in Scheme 1), and that at ambient temperature there is facile rotation around the C(3^{IV})–C(4^{IV}) bond of the butadiene residue, which is explicable by the fact that in the “push-pull” ketene amins of this type all three C–C bonds of the butadiene chain are equalized due to electron delocalization.

However, the ambient-temperature (296 K) ¹H and ¹³C NMR spectra of the homologous compound **33** show the presence of two sets of analogous signals with nearly equal intensity, which clearly indicates that at this temperature in solution ([D₆]DMSO) compound **33** exists in two almost equally populated slowly interchangeable rotameric forms. The presence of a methylene linker group at C(1^I) in this compound keeps the plane of the attached ketene amina moiety nearly parallel to the C(1^I)–OMe bond axis, which apparently strongly restricts the free rotation around the C(2^I)–C(2^{IV}) bond at ambient temperature. Here again, the long range correlation between both NMe₂ groups with carbon atom C(4^{IV}) confirms the ketene amina structure of compound **33**.

The addition of cyanoacetamide to the THF solutions of orthoamides **22** and **23** at r.t. causes instant deep yellow-orange colorization of the mixtures. Presumably this is a result of the rapid formation of the ketene amins **34** and **35**, respectively. However, in both cases the TLC analyses of the reaction mixtures showed, beside the intensively yellow ketene amina spots, the presence of colorless products as single spots of blue fluorescence at 365 nm. After longer reaction times at r.t., the initial concentration of the yellow ketene amina decreased at the expense of a constantly increasing concentration of the colorless products. Due to their spontaneous transformation, the isolation of the initial ketene amins **34** and **35** was impossible. Therefore the solvent (THF) was removed under reduced pressure, replaced by 2-propanol, and the mixtures were heated for additional 2 h at 80 °C for completion of the reaction. The elemental analyses and MS spectra of the isolated colorless terminal products were consistent with the expected 2-pyridone derivatives **36** and **37**. However, since cyanoacetamide is an unsymmetrical 1,3-bis-nucleophile with CH₂ and NH₂ acidic groups, under the strongly basic reaction conditions two plausible constitutional isomeric 2-pyridone structures for the products **36** and **37** were possible (Scheme 3, square and round brackets). The ¹H NMR spectra confirmed the presence of 2-pyridone moieties



Scheme 3. Synthesis of orthoamides **22** and **23** and their condensation reactions with different nucleophiles. Some of the H atoms are omitted for clarity. *Reagents and conditions:* (a) 1) *n*-BuLi, THF, $-40^\circ\text{C} \rightarrow \text{r.t.}$, 2) hexamethylguanidinium chloride (**2**), 7 d, r.t.; (b) $R(=\text{NH})\text{NH}_2$, THF, 65°C , 3 h; (c) malononitrile, THF, 24 h, r.t.; (d) cyanoacetamide, 1) THF, 24 h, r.t., 2) 2-PrOH, 80°C , 2 h; (e) EtOH-aq. 37% HCl, 48 h, r.t. *Note:* In order to unify the description and discussion of the stereochemical and spectroscopic features, in both series of homologous *cis*-2,4,7,9-tetraoxabicyclo[4.4.0]decane-derived binary conjugates presented here, the conjunctive C atom is labelled as C(1¹). However, in compounds **25**, **27**, **29**, **31**, **33**, and **37**, this atom is part of an conjunctive ethyl chain and according to the UPAC nomenclature should be correctly numbered as C(2¹). The correct UPAC names of those compounds are given with the corresponding procedures in the Experimental Section.

in both compounds **36** and **37** displaying C(5^{IV})H (at $\delta = 5.87$ and 5.65 ppm, respectively), NH (at 11.27 and 11.13 ppm, respect.), and NMe₂ (at 3.05 and 2.95 ppm, respect.) signals. The infrared spectra, containing bands for C \equiv N (at 2208 and 2211 cm⁻¹) and C=O groups (at 1599 and 1603 cm⁻¹) were also in full agreement with the 2-pyridone structures but not sufficient to distinguish between the two possible isomers for compounds **36** and **37**. Surprisingly, at this point we were confronted with a problem that was nonsolvable by 2D NMR techniques, because in the ¹³C NMR spectra of both compounds the signals for the C atoms of the 2-pyridone moieties were missing. Only very weak signals of CN groups were observed. The NMe₂ signals were overlapped by the solvent ([D₆]DMSO) signal. According to consulted NMR experts, the problem was attributed to a cross-relaxation phenomenon. However, the registration of the ¹³C NMR spectra of compounds **36** and **37** with longer relaxation times from 1 s to 10 and 20 s and a larger number of scans, as recommended, did not improve the signal intensity. Spectral comparison with unsubstituted- and 4-phenyl-substituted 2-pyridone [17] and 4-methyl-6-dimethylamino-2-pyridone and 4-dimethylamino-6-methyl-2-pyridone [40] was not sufficient for the unambiguous structural identification of compounds **36** and **37**.

The treatment of compounds **36** and **37** with an ethanol-aq. 37% HCl mixture for 48 h at r.t. yielded the unprotected open-chain nucleoside analogs, namely the L-xylose derivative **38** and the 6-deoxy-D-sorbitol derivative **39**, respectively. Fortunately, the ¹³C NMR spectra of compounds **38** and **39** clearly display all C atom signals of the 2-pyridone moieties, which were completely assigned by 2D NMR techniques. The evident long range heteronuclear correlations between C(5)H and C(5^I)H with C(3^I) in the case of compound **38** and between C(6)H₂ and C(5^I)H with C(3^I) in the case of compound **39** unquestionably demonstrated that in both **38** and **39** and their parent compounds **36** and **37** the 2-pyridone ring is attached to the sugar moieties at the C(4) position, as shown in Scheme 3. This fact illuminates the complete pattern of the reactions of orthoamides **22** and **23** with cyanoacetamide, which apparently involves initial nucleophilic attack from the cyanoacetamide acidic CH₂ group exclusively at the β -C atom of the orthoamides **22** and **23** (which unambiguously proves the ketene aminal structures of the transient intermediates **34** and **35**) and

secondary ring closure reactions from the amide NH₂ groups to the terminal ketene aminal groups of the transient **34** and **35**. These reactions presumably operate *via* intermediate C(2^{IV})-C(3^{IV})-*s-cis* conformers (not shown) of the corresponding ketene aminals **34** and **35**.

In conclusion, the present study has demonstrated the applicability of alkynecarboxylic acid orthoamide chemistry as a potent road for the synthesis of a new type of C-C bond sugar-conjugated heterocyclic compounds of potential biomedical interest. We have shown this with 2,4,3,5-bis(4-methoxybenzylidene)-protected L-xylose as a model compound, but variations in the appropriately protected sugar derivatives are possible. Some of the new conjugated compounds reported herein were submitted for biological screening. The tests are in progress.

Experimental Section

General procedures

FT-IR spectra were recorded on a Perkin-Elmer 457 instrument. NMR spectra were recorded on Bruker AC 250 (operating at 250.13 MHz for ¹H and at 62.9 MHz for ¹³C) or Bruker ARX 500 (operating at 500.1 MHz for ¹H and 125.7 MHz for ¹³C) instruments. The spectra were calibrated using the solvent signal according to [41] or TMS as internal standard unless stated otherwise. For the assignment of ¹H and ¹³C NMR signals, DEPT and two-dimensional ¹H,¹H-COSY, ¹H, ¹³C correlation spectra (HSQC and HMBC) were recorded. Analytical thin-layer chromatography (TLC) was performed on pre-coated POLYGRAM[®] SIL G/UV₂₅₄ plastic sheets (Machery-Nagel), detection by UV light. Column chromatography was carried out on silica gel 60 (0.063–0.20 mm), Machery-Nagel. Melting points were determined with a Büchi 510 apparatus (Büchi Laboratoriumstechnik AG, Flawil/Switzerland) and are uncorrected. Elemental analyses were performed by the service of the Institut für Organische Chemie, University of Stuttgart. ESI-MS spectra were measured on a micrOTOF-Q (Bruker Daltonics) instrument. Solvents and liquid reagents were purified and dried according to recommended procedures.

(1*R*)-1-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-ethane-1,2-diol (**11**)

A mixture of D-sorbitol (**10**, 80 g, 0.44 mol), 4-methoxybenzaldehyde (240 g, 1.8 mol), and acetic acid (800 mL) was stirred at 70 °C until a clear solution was obtained, and then at r.t. for 48 h. Ether (*ca.* 200 mL) was added. The jelly-like material was suspended, isolated by filtration, washed several times with an aqueous solution of K₂CO₃

and with hot water and air-dried overnight to yield compound **11**. Yield 102 g (56%), colorless powder; m. p. 220–222 °C (lit.: m. p. 185–187 °C [36]). – $R_f = 0.5$ (CHCl₃-dioxane, 1 : 1). – FT-IR (ATR): $\nu = 3514$ (OH), 3311 (OH assoc.), 2972, 2932, 2837, 1614, 1517, 1246, 1089, 1061, 1035, 979, 825, 778, 660 cm⁻¹. – ¹H NMR (250 MHz, [D₆]DMSO): $\delta = 7.39$ and 7.37 [2d, $J = 8.5$ Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.92 [d, $J = 8.6$ Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.59 [s, 2H, C(3)H and C(8)H], 4.82 [d, $J = 5.4$ Hz, 1H, C(1^I)OH], 4.41 (t, $J = 5.6$ Hz, 1H, C(2^I)OH], 4.23 – 4.13 [m, 3H, C(1)H + C(10)H₂], 3.89 [bs, 1H, C(6)H], 3.84 – 3.65 [m, 8H, C(5)H, C(1^I)H and 2 ArOCH₃ as s at 3,75 ppm], 3.64 – 3.52 [m, 1H, C(2^I)Ha], 3.48 – 3.37 [m, 1H, C(2^I)Hb]. – ¹³C NMR (62.89 MHz, [D₆]DMSO): $\delta = 159.37$, 159.32 [C(4^{II}) and C(4^{III})], 131.16 , 130.90 [C(1^{II}) and C(1^{III})], 127.47 , 127.43 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.25 , 113.19 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.25 , 99.20 [C(3) and C(8)], 77.58 [C(5)], 69.95 [C(1)], 69.24 [C(10)], 68.27 [C(6)], 67.67 [C(1^I)], 62.58 [C(2^I)], 55.08 (OCH₃). – C₂₂H₂₆O₈ (418.43): calcd. C 63.15, H 6.26; found C 63.04, H 6.21.

(1*S*,3*S*,5*S*,6*R*,8*R*)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decane-5-carboxaldehyde (**13**)

A solution of NaIO₄ (18 g, 84 mmol) in water (160 mL) was added to a stirred suspension of finely powdered compound **11** (25 g, 60 mmol) in 80% aqueous dioxane (500 mL). Compound **11** gradually dissolved, and simultaneously the product (compound **12**) began to crystallize. After 48 h stirring at r. t., the resulting suspension was filtered. The colorless crystalline product was washed with water and air-dried. The obtained aldehyde hydrate **12** was suspended in 400 mL of toluene and the mixture was refluxed with a Dean-Stark trap until complete removal of the water. The hot toluene solution was quickly filtered and left overnight at r. t. The resulting suspension was filtered, the solid material was washed with toluene and dried to yield aldehyde **13**. Yield 19.83 g (86%), colorless crystalline powder; m. p. 186–188 °C (lit.: m. p. 167–168 °C [36]). – $R_f = 0.23$ (CHCl₃-THF, 10 : 0.5). – FT-IR (ATR): $\nu = 2968$, 2933 , 2838 , 1736 (C=O), 1614 , 1585 , 1515 , 1401 , 1168 , 1246 , 1096 , 1065 , 1032 , 993 , 829 , 815 cm⁻¹. – ¹H NMR (250 MHz, [D₆]DMSO): $\delta = 9.56$ (s, 1H, CH=O), 7.45 and 7.30 [2d, $J = 8.6$ Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.97 and 6.91 [2d, $J = 8.7$ Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.73 and 5.61 [2s, 2H, C(3)H and C(8)H], 4.75 [bd, $J = 2$ Hz, 1H, C(5)H], 4.51 [bt, $J = 1.7$ Hz, 1H, C(6)H], 4.15 [bt, $J = 14.0$ Hz, 2H, C(10)H₂], 4.00 [s, 1H, C(1)H], 3.76 and 3.74 (2s, 6H, 2 ArOCH₃). – ¹³C NMR (62.89 MHz, [D₆]DMSO): $\delta = 199.49$ (C=O), 159.65 and 159.48 [C(4^{II}) and C(4^{III})], 130.51 and 130.23 [C(1^{II}) and C(1^{III})], 127.74 and 127.37 [C(2^{II}), C(6^{II})],

C(2^{III}), C(6^{III})], 113.38 and 113.32 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.31 and 98.88 [C(3) and C(8)], 81.57 [C(5)], 69.38 [C(1)], 69.02 [C(10)], 68.95 [C(6)], 55.13 and 55.08 (2 ArOCH₃). – C₂₁H₂₂O₇ (386.39): calcd. C 65.28, H 5.74; found C 65.22, H 5.76.

(1*S*)-1-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decane-5-yl]-1-hydroxy-prop-2-yne (**14**) and (1*R*)-1-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decane-5-yl]-1-hydroxy-prop-2-yne (**15**)

A 0.6 M toluene/THF solution of ethynylmagnesium chloride (80 mL, 48 mmol) was added slowly at r. t. under N₂ atmosphere to a suspension of finely powdered aldehyde **13** (16.8 g, 43.5 mmol) in anhydrous THF (10 mL). The resulting clear, yellowish solution was stirred at r. t. for additional 2.5 h, then poured into a 1.5% aqueous solution of NH₄Cl (1 L). The precipitated material was isolated by filtration, washed with water and air-dried. The resulting slightly yellowish powder (20 g, water wet) was a mixture of the epimers **14** and **15**. The presence of water in this material seems to play an important role for the following separation of the epimers by recrystallization from methanol. Therefore the still water-wet crystalline mixture of compounds **14** and **15** was refluxed for 1 h in methanol (1 L). The resulting suspension was cooled to r. t. and filtered. The collected solid material (6.15 g) was once again refluxed for 1 h in methanol (250 mL), isolated by filtration, washed with methanol and dried to yield the pure epimer **14**. The methanol mother liquor from the separation of the epimers was concentrated under reduced pressure. Toluene (300 mL) was added to the solid residue, and the mixture was refluxed with a Dean-Stark trap for removal of the residual water. The clear yellow solution was left at r. t. The crystallized material was collected by filtration, washed with toluene and dried to yield the pure compound **15**.

Data for compound **14**: Yield 4.88 g (27%), colorless crystals; m. p. 232–234 °C. – $R_f = 0.53$ (CHCl₃-THF, 9 : 1). – FT-IR (ATR): $\nu = 3280$ (OH assoc.), 2964 , 2932 , 2896 , 2835 (OCH₃), 1615 , 1585 , and 1515 (Ar), 1247 (C=C-O), 1170 , 1091 , 1028 , 832 cm⁻¹. – ¹H NMR (250 MHz, [D₆]DMSO): $\delta = 7.41$ and 7.34 [2d, $J = 8.8$ Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.94 and 6.93 [2d, $J = 8.8$ Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.65 [d, $J = 6.0$ Hz, 1H, OH], 5.62 [s, 1H, C(3)H], 5.56 (s, 1H, C(8)H), 4.45 – 4.34 [m, 1H, C(1^I)H], 4.24 – 4.02 [m, 3H, C(1)H and C(10)H₂], 3.97 – 3.83 [m, 2H, C(5)H and C(6)H], 3.75 (s, 6H, 2 OCH₃), 3.45 [d, $J = 2.0$ Hz, 1H, C≡CH]. – ¹³C NMR (62.89 MHz, [D₆]DMSO): $\delta = 159.49$ and 159.40 [C(4^{II}) and C(4^{III})], 130.86 and 130.62 [C(1^{II}) and C(1^{III})], 127.75 and 127.18 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.35 and 113.24 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.37 [C(3)], 99.20 [C(8)], 82.41

[C(2^I)], 80.56 [C(5)], 75.98 [C(3^I)], 69.45 and 69.35 [C(1) and C(6)], 69.06 [C(10)], 60.49 [C(1^I)], 55.10 (ArOCH₃). – C₂₃H₂₄O₇ (412.43): calcd. C 66.98, H 5.87; found C 65.31, H 5.87.

Data for compound 15: Yield 8.69 g (48.5%), colorless, cotton-like crystals; m. p. 160–162 °C. – *R*_f = 0.43 (CHCl₃-THF, 9 : 1). – FT-IR (ATR): ν = 3495 and 3299 (OH asoc.), 2970, 2935, 2912, 2837 (OCH₃), 1614, 1586, and 1516 (Ar), 1245 (C=C-O), 1170, 1090, 1030, 828, 778 cm⁻¹. – ¹H NMR (250 MHz, [D₆]DMSO): δ = 7.39 and 7.38 [2d, *J* = 8.7 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.94 and 6.93 [2d, *J* = 8.8 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.86 (d, *J* = 6.4 Hz, 1H, OH), 5.67 [s, 1H, C(3)H], 5.59 [s, 1H, C(8)H], 4.44–4.34 [m, 1H, C(1^I)H], 4.2–4.03 [m, 3H, C(6)H and C(10)H₂], 3.95–3.84 [m, 2H, C(1)H and C(5)H], 3.75 (s, 6H, 2 ArOCH₃), 3.23 (d, *J* = 2.0 Hz, 1H, C≡CH). – ¹³C NMR (62.89 MHz, [D₆]DMSO): δ = 159.49 and 159.39 [C(4^{II}) and C(4^{III})], 130.97 and 130.65 [C(1^{II}) and C(1^{III})], 127.55 and 127.44 [C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 113.33 and 113.27 [C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 99.33 [C(3)], 99.24 [C(8)], 84.87 [C(2^I)], 79.55 [C(5)], 74.90 [C(3^I)], 69.57 [C(1)], 69.11 [C(10)], 67.65 [C(6)], 58.01 [C(1^I)], 55.11 (ArOCH₃). – C₂₃H₂₄O₇ (412.43): calcd. C 66.98, H 5.87; found C 66.94, H 5.90.

(1R)-1-[(1S,3S,5R,6R,8R)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-1-hydroxybut-3-yn-1-yl (16)

An 80% toluene solution of propargyl bromide (11.8 mL, 9.44 g, 80 mmol) was added to a suspension of compound **13** in a DMF-diethyl ether (1 : 1) mixture (230 mL). Zn powder (7.8 g, 120 mmol), previously quickly washed with 2 N aqueous HCl, several times with water and dried at 200 °C under N₂ for 1 h, was added in small portions to the reaction mixture under stirring at r. t. After the addition of *ca.* 1/6 of the Zn powder, the reaction mixture was gently warmed briefly with a fan heater, which initialized an exothermic reaction. The remaining metal powder was added slowly to prevent the reflux of the reaction mixture (less than 35 °C, if necessary the mixture should be externally cooled with ice water). After the addition of the whole amount of Zn powder, the mixture was stirred at r. t. for additional 2 h, then filtered through Celite® and the Celite® washed with DMF. The yellow-orange filtrate was poured into a 4% aqueous solution of NH₄Cl (1 L). The precipitated yellowish solid was collected by filtration, washed with water and 70% aqueous ethanol and air dried to yield the crude compound **16** as an ochre-colored powder (16 g, 97%). The product was further purified by recrystallization from toluene to yield the pure compound **16**. Yield 13.9 g (84%), colorless crystals; m. p. 190–192 °C. – *R*_f = 0.45 (CHCl₃-THF, 10 : 1). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.39 and 7.38 [2d, *J* = 8.6 Hz,

4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.93 and 6.92 [2d, *J* = 8.8 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.60 [bs, 2H, C(3)H and C(8)H], 5.28 (d, *J* = 6.0 Hz, 1H, OH), 4.19–4.09 [m, 3H, C(6)H + C(10)H₂], 3.92–3.84 [m, 2H, C(1)H, C(1^I)H], 3.79–3.69 [m, 7H, C(5)H and 2 ArOCH₃ (s at 3.75 ppm)], 2.73 (bt, *J* = 2.5 Hz, 1H, C≡CH), 2.46 [dt, *J* = 17.0, 2.7 Hz, 1H, C(2^I)Ha], 2.30 and 2.28 [2dd, *J* = 17.0, 2.6 Hz, 1H, C(2^I)Hb]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 159.42 and 159.35 [C(4^{II}) and C(4^{III})], 131.08 and 130.74 [C(1^{II}) and C(1^{III})], 127.43 and 127.41 [C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 113.31 and 113.22 [C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 99.33 and 99.28 [C(3) and C(8)], 82.08 [C(3^I)], 79.43 [C(5)], 72.03 [C(4^I)], 69.82 [C(1)], 69.19 [C(10)], 68.10 [C(6)], 64.90 [C(1^I)], 55.10 and 55.08 (2 ArOCH₃), 23.36 [C(2^I)]. – C₂₄H₂₆O₇ (426.46): calcd. C 67.59, H 6.15; found C 67.35, H 6.17.

(1S)-1-[(1S,3S,5R,6R,8R)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-1-prop-2-yn-1-yl 4-nitrobenzoate (17)

4-Nitrobenzoyl chloride (250 mg, 1.35 mmol) was added to a mixture of the alkynol **14** (500 mg, 1.2 mmol), triethylamine (3 mL), and acetonitrile (25 mL), and the mixture was stirred at r. t. overnight. The crystalline material was collected by filtration, washed with methanol and dried. The crude product was recrystallized from toluene to yield pure compound **17**. Yield 490 mg (72%), pale-yellow cotton-like crystals; m. p. 244–246 °C. – *R*_f = 0.43 (CHCl₃-THF, 10 : 0.2). – FT-IR (ATR): ν = 3269 (C≡CH), 2955, 2840 (OCH₃), 1734 (C=O), 1613 and 1585 (Ar), 1516 (Ar and NO₂), 1278 (NO₂), 1249 (C=C-O), 1167, 1090, 1032, 827, 715 cm⁻¹. – ¹H NMR (500 MHz, [D₆]DMSO): δ = 8.35 (d, *J* = 8.8 Hz, 2H, 4-NO₂-Ph, *m*-H), 8.17 (d, *J* = 8.8 Hz, 2H, 4-NO₂-Ph, *o*-H), 7.34 and 7.30 [2d, *J* = 8.8 Hz, 4H, C(2^{II})H, C(6^{II})H, and C(2^{III})H, C(6^{III})H], 6.93 and 6.87 [2d, *J* = 8.8 Hz, 4H, C(3^{II})H, C(5^{II})H, and C(3^{III})H, C(5^{III})H], 5.85 and 5.84 [dd, *J* = 8.8, 2 Hz, 1H, C(1^I)H], 5.72 [s, 1H, C(3)H], 5.65 [s, 1H, C(8)H], 4.51 and 4.50 [dd, *J* = 8.9, 1.9 Hz, 1H, C(5)H], 4.33 [bs, 1H, C(6)H], 4.24 [d, *J* = 12.8 Hz, 1H, C(10)Ha], 4.17 [d, *J* = 12.8 Hz, 1H, C(10)Hb], 4.04 [s, 1H, C(1)H], 3.90 [d, *J* = 2.0 Hz, 1H, C≡CH], 3.75 and 3.70 (2s, 6H, 2 ArOCH₃). – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 163.39 (C=O), 159.49 [C(4^{II}) and C(4^{III})], 150.47 [4-NO₂-Ph, C(4)], 134.12 [4-NO₂-Ph, C(1)], 130.79 [4-NO₂-Ph, C(2) and C(6)], 130.56 and 130.12 [C(1^{II}) and C(1^{III})], 127.33 and 127.20 [C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 124.05 [4-NO₂-Ph, C(3) and C(5)], 113.41 and 113.28 [C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 99.31 [C(8)], 98.98 [C(3)], 79.19 [C(2^I)], 77.53 [C(5)], 76.78 [C(3^I)], 69.18 [C(1)], 69.00 [C(6)], 68.96 [C(10)], 64.33 [C(1^I)], 55.07 (ArOCH₃). – C₃₀H₂₇NO₁₀ (561.53): calcd. C 64.17, H 4.85, N 2.49; found C 64.05, H 4.86, N 2.42.

(1R)-1-[(1S,3S,5R,6R,8R)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-1-prop-2-yne-1-yl 4-nitrobenzoate (18)

4-Nitrobenzoyl chloride (400 mg, 2.16 mmol) was added to a mixture of the alkynol **15** (800 mg, 1.94 mmol), triethylamine (3 mL), and acetonitrile (20 mL), and the mixture was stirred at r. t. overnight. A 10% aqueous solution of NH₄Cl (20 mL) was added, the mixture was extracted with CHCl₃, the organic extract was washed with water and concentrated under reduced pressure. The crystalline residue was dissolved in boiling ethanol (*ca.* 250 mL). After cooling to r. t. the crystallized product was collected by filtration to yield compound **18**, which was recrystallized from toluene. Yield 800 mg (73%), yellowish fine needles; m. p. 206–208 °C. – *R*_f = 0.43 (CHCl₃-THF, 10 : 0.2). – FT-IR (ATR): ν = 3294 (C≡CH), 2890, 2834 (OCH₃), 1727 (C=O), 1613 and 1586 (Ar), 1530 and 1518 (Ar and NO₂), 1272 and 1244 (C=C-O and NO₂), 1172, 1100, 1033, 997, 832, 778, 713 cm⁻¹. – ¹H NMR (500 MHz, [D₆]DMSO): δ = 8.34 [d, *J* = 8.8 Hz, 2H, 4-NO₂-Ph, *m*-H], 8.24 [d, *J* = 8.8 Hz, 2H, 4-NO₂-Ph, *o*-H], 7.40 and 7.22 [2d, *J* = 8.8 Hz, 4H, C(2^{II})H, C(6^{II})H, and C(2^{III})H, C(6^{III})H], 6.95 and 6.90 [2d, *J* = 8.8 Hz, 4H, C(3^{II})H, C(5^{II})H, and C(3^{III})H, C(5^{III})H], 5.80 [s, 1H, C(3)H], 5.75 and 5.74 [dd, *J* = 8.8, 2.0 Hz, C(1^I)H], 5.50 [s, 1H, C(8)H], 4.55 and 4.54 [dd, *J* = 8.8, 2.0 Hz, C(5)H], 4.23 [bs, 1H, C(6)H], 4.15 [bs, 2H, C(10)H₂], 4.02 [s, C(1)H], 3.76 and 3.75 [2s, 6H, 2 ArOCH₃], 3.69 [d, *J* = 2.0 Hz, C≡CH]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 162.75 (C=O), 159.55 and 159.28 [C(4^{II}) and C(4^{III})], 150.52 [4-NO₂-Ph, C(4)], 133.89 [4-NO₂-Ph, C(1)], 130.88 (4-NO₂-Ph, C(2)H and C(6)H), 130.46 and 130.11 [C(1^{II}) and C(1^{III})], 127.47 and 126.94 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 123.93 [4-NO₂-Ph, C(3)H and C(5)H], 113.34 and 113.22 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.33 [C(3)], 98.87 [C(8)], 78.89 [C(2^I)], 77.97 [C(5)], 76.89 [C(3^I)], 69.14 [C(1)], 68.88 [C(10)], 67.65 [C(6)], 61.76 [C(1^I)], 55.05 and 54.99 (2 ArOCH₃). – C₃₀H₂₇NO₁₀ (561.53): calcd. C 64.17, H 4.85, N 2.49; found C 64.86, H 4.98, N 2.36.

(1R)-1-[(1S,3S,5R,6R,8R)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-1-but-3-yne-1-yl 4-nitrobenzoate (19)

4-Nitrobenzoyl chloride (250 mg, 1.35 mmol) was added to a mixture of homoalkynol **16** (500 mg, 1.17 mmol), triethylamine (3 mL), and acetonitrile (20 mL), and the mixture was stirred at r. t. overnight. The solvent was removed at reduced pressure. The solid residue was suspended in methanol. The crystalline material was collected by filtration, washed with methanol and dried to yield compound **19**, which was recrystallized from acetonitrile. Yield

490 mg (72%), slightly pink fine needles; m. p. 196–198 °C. – *R*_f = 0.58 (CHCl₃-THF, 10 : 0.2). – FT-IR (ATR): ν = 3271 (C≡CH), 2933, 2841 (OCH₃), 1739 (C=O), 1608 and 1586 (Ar), 1531 and 1516 (Ar and NO₂), 1346, 1245 (NO₂), 1225 (C=C-O), 1092, 1027, 1010, 827, 778, 719 cm⁻¹. – ¹H NMR (500 MHz, [D₆]DMSO): δ = 8.37 [d, *J* = 8.8 Hz, 2H, 4-NO₂-Ph, *m*-H], 8.23 [d, *J* = 8.8 Hz, 2H, 4-NO₂-Ph, *o*-H], 7.40 and 7.27 [2d, *J* = 8.8 Hz, 4H, C(2^{II})H, C(6^{II})H, and C(2^{III})H, C(6^{III})H], 6.94 and 6.91 [2d, *J* = 8.8 Hz, 4H, C(3^{II})H, C(5^{II})H, and C(3^{III})H, C(5^{III})H], 5.74 [s, 1H, C(3)], 5.51 [s, 1H, C(8)], 5.47–5.42 [m, 1H, C(1^I)H], 4.42 and 4.41 [dd, *J* = 8.8, 1.7 Hz, C(5)H], 4.16 [s, 1H, C(6)H], 4.14 [bs, 2H, C(10)H₂], 4.02 [bs, 1H, C(1)H], 3.76 and 3.75 [2s, 6H, 2 ArOCH₃], 2.90 [t, *J* = 2.5 Hz, 1H, C≡CH], 2.83 [dt, *J* = 17.0, 2.7 Hz, 1H, C(2^I)Ha], 2.74 and 2.73 [2dd, *J* = 17.0, 2.7 Hz, 1H, C(2^I)Hb]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 163.08 (C=O), 159.47 and 159.23 [C(4^{II}) and C(4^{III})], 150.36 [4-NO₂-Ph, C(4)], 134.61 [4-NO₂-Ph, C(1)], 130.71 [4-NO₂-Ph, C(2) and C(6)], 130.56 and 130.20 [C(1^{II}) and C(1^{III})], 127.38 and 126.94 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 123.92 (4-NO₂-Ph, C(3) and C(5)), 113.30 and 113.18 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.30 [C(3)], 98.81 [C(8)], 79.30 [C(3^I)], 76.37 [C(5)], 73.26 [C(4^I)], 69.30 [C(1^I)], 69.05 [C(1)], 68.88 [C(10)], 68.04 [C(6)], 55.04 and 54.99 (2 ArOCH₃), 20.29 [C(2^I)]. – C₃₁H₂₉NO₁₀ (575.56): calcd. C 64.69, H(5.08), N 2.43; found C 62.61, H 5.20, N 2.37.

(1R)-1-[(1S,3S,5R,6R,8R)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-1-methoxy-prop-2-yne (20)

NaH (60% paraffin suspension, 1.85 g, 1.11 g NaH, 46 mmol) was added in small portions at r. t. under N₂ to a stirred mixture of compound **15** (15.9 g, 38.6 mmol) and MeI (10.5 g, 74 mmol) in anhydrous DMF (75 mL). The mixture was stirred for additional 3 h at r. t., then poured into cold water (150 mL). The precipitate was collected by filtration, washed with water, and air-dried. The obtained yellowish solid was suspended in methanol (400 mL) and the suspension refluxed for 1 h. After cooling to r. t., the crystalline material was collected by filtration, washed with methanol and diethyl ether and dried to yield compound **8**. Yield 15 g (91%), colorless crystals; m. p. 176–178 °C. – *R*_f = 0.65 (CHCl₃-THF, 10 : 0.2). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.38 and 7.36 [2d, *J* = 8.6 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.94 and 6.93 [2d, *J* = 8.9 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.69 [s, 1H, C(3)H], 5.62 [s, 1H, C(8)H], 4.20 and 4.19 [dd, *J* = 9.5, 2.0 Hz, 1H, C(1^I)H], 4.13 [bt, 2H, *J* = 15 Hz, C(10)H₂], 4.07–4.02 [m, 2H, C(5)H and C(6)H], 3.92 [bs, 1H, C(1)H], 3.75 [s, 6H, 2 ArOCH₃], 3.42 [d, *J* = 2.0 Hz, 1H, C≡CH], 3.35 [s, 3H, C(1^I)OCH₃]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ =

159.52 and 159.37 [C(4^{II}) and C(4^{III})], 130.85 and 130.47 [C(1^{II}) and C(1^{III})], 127.51 and 127.21 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.36 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.33 [C(3)], 99.08 [C(8)], 81.06 [C(2^I)], 77.81 [C(5)], 77.36 [C(3^I)], 69.38 [C(1)], 69.06 [C(10)], 67.87 and 67.83 [C(1^I) and C(6)], 56.44 [C(1^I)OCH₃], 55.11 and 55.07 (2 ArOCH₃). – C₂₄H₂₆O₇ (426.46): calcd. C 67.59, H 6.15; found C 67.31, H 6.13.

(1*R*)-1-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-1-methoxybut-3-yne (**21**)

NaH (60% paraffin suspension, 0.46 g, 0.276 g NaH, 11.5 mmol) was added in small portions under stirring in N₂ atmosphere at r. t. to a mixture of compound **16** (4.38 g, 10.3 mmol) and MeI (2.9 g, 20 mmol) in anhydrous DMF (30 mL), and the mixture was stirred for additional 3 h at r. t. The product separated from the reaction mixture as colorless crystals. Water (150 mL) was added and the suspension was filtered. The product was washed with water and methanol and dried to yield compound **21**, which was recrystallized from ethyl acetate. Yield 4.25 g (94%), colorless cotton-like crystals; m. p. 196–198 °C. – *R*_f = 0.29 (CHCl₃-THF, 10 : 0.2). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.36 [d, *J* = 8.7 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.92 and 6.93 [2d, *J* = 8.7 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.65 [s, 1H, C(8)H], 5.61 [s, 1H, C(3)H], 4.15 [bt, 2H, *J* = 15 Hz, C(10)H₂], 4.10 [bs, 1H, C(6)H], 3.95 [bs, 1H, C(1)H], 3.91 and 3.90 [dd, *J* = 8.9, 1.6 Hz, 1H, C(5)H], 3.75 [s, 6H, 2 ArOCH₃], 3.62–3.56 [m, 1H, C(1^I)H], 3.37 [s, 3H, C(1^I)OCH₃], 2.78 [bt, *J* = 2.6 Hz, 1H, C≡CH], 2.64 [dt, *J* = 17.0, 2.9 Hz, 1H, C(2^I)Ha], 2.31 and 2.30 [2dd, *J* = 17.0, 2.7 Hz, 1H, C(2^I)Hb]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 159.36 and 159.26 [C(4^{II}) and C(4^{III})], 130.84 and 130.48 [C(1^{II}) and C(1^{III})], 127.30 and 127.10 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.28 and 113.24 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.27 [C(3)], 98.99 [C(8)], 81.10 [C(3^I)], 77.48 [C(5)], 74.80 [C(1^I)], 72.16 [C(4^I)], 69.55 [C(1)], 69.05 [C(10)], 68.21 [C(6)], 57.76 [C(1^I)OCH₃], 55.02 and 54.98 (2 ArOCH₃), 19.42 [C(2^I)]. – C₂₅H₂₈O₇ (440.48): calcd. C 68.17, H 6.41; found C 67.50, H 6.36.

Preparation of THF solutions of (1*R*)-1-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-1-methoxy-4,4,4-tris(dimethylamino)but-2-yne (**22**) and (1*R*)-1-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]-1-methoxy-5,5,5-tris(dimethylamino)pent-3-yne (**23**) – general procedure

A hexane solution (1.6 M) of *n*-BuLi (15 mL, 24 mmol) was added dropwise under N₂ at –40 °C to a solution of alkyne **20** (10 g, 23 mmol) or alkyne **21** (10.1 g, 23 mmol) in

anhydrous THF (250 mL). The mixture was stirred at –40 °C for 30 min, then left to warm to r. t. The yellowish solution was transferred under N₂ through a connecting glass tube to a flask containing previously dried (110 °C, 0.1 Torr, 2 h) finely powdered hexamethylguanidinium chloride (**2**, 8.3 g, 46 mmol). The suspension was stirred at r. t. under N₂ for 7 days. Aliquots from the resulting stock solutions of orthoamide **22** or **23** were used in the following syntheses.

6-Dimethylamino-4-[(*R*)-methoxy-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]methyl]-2-methyl-pyrimidine (**24**)

Acetamide hydrochloride (0.3 g, 3 mmol) was added to a solution obtained by addition of Na metal (70 mg, 3 mmol) to ethanol (20 mL). The mixture was stirred at r. t. for 20 min, then the solvent was removed under reduced pressure. A solution of the orthoamide **22** (792 mg, 1.4 mmol) in THF (16 mL) was added under N₂ to the residue, and the mixture was stirred at 65 °C for 3 h. Water was added and the mixture was extracted twice with CHCl₃. The organic extract was washed twice with water and concentrated under reduced pressure. The foam-like residue was dissolved in a minimum amount of CHCl₃ and purified by flash chromatography on silica gel. The product was eluted consecutively with CHCl₃, CHCl₃-ethyl acetate (1 : 1), ethyl acetate, ethyl acetate-methanol (95 : 5). After the evaporation of the eluate the residue was triturated with diethyl ether, the solid material was collected by filtration, washed with diethyl ether and dried to yield compound **24**. Yield 530 mg (70%), colorless crystals; m. p. 192–194 °C. – *R*_f = 0.24 (ethyl acetate). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.41 and 7.18 [2d, *J* = 8.8 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.96 and 6.84 [2d, *J* = 8.7 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 6.52 [s, 1H, C(5^{IV})H], 5.68 [s, 1H, C(8)H], 5.52 [s, 1H, C(3)H], 4.37 and 4.38 [dd, *J* = 9.25, 1.5 Hz, C(5)H], 4.23 [d, *J* = 9.25 Hz, C(1^I)H], 4.20 [s, 1H, C(6)H], 4.19–4.12 [m, 2H, C(10)H₂], 3.96 [s, 1H, C(1)H], 3.76 and 3.70 [2s, 6H, 2ArOCH₃], 3.18 [s, 3H, C(1^I)OCH₃], 3.00 [s, 6H, N(CH₃)₂], 2.36 [s, 3H, C(2^{II})CH₃]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 165.84 [C(2^{IV})], 164.08 [C(4^{IV})], 162.12 [C(6^{IV})], 159.36 [C(4^{II}) and C(4^{III})], 131.03 and 130.55 [C(1^{II}) and C(1^{III})], 127.33 and 127.25 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.35 and 113.20 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.59 [C(5^{IV})], 99.15 and 99.10 [C(3) and C(8)], 79.72 [C(1^I)], 77.89 [C(5)], 69.67 [C(1)], 69.23 [C(10)], 68.58 [C(6)], 56.87 [C(1^I)OCH₃], 55.08 and 55.05 (2 ArOCH₃), 36.55 [N(CH₃)₂], 25.95 [C(2^{IV})CH₃]. – C₂₉H₃₅N₃O₇ (537.60): calcd. C 64.79, H 6.56, N 7.82; found C 64.57, H 6.58, N 6.73. – HRMS ((+)ESI): *m/z* = 538.2552 (calcd. 538.2553 for C₂₉H₃₆N₃O₇, [M+H]⁺).

6-Dimethylamino-4-[(2*R*)-2-methoxy-2-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]ethyl]-2-methyl-pyrimidine (**25**)

Acetamidine hydrochloride (470 mg, 5 mmol) was added to a solution obtained by addition of Na metal (120 mg, 5.2 mmol) to ethanol (10 mL). The mixture was stirred at r. t. for 20 min, then the solvent was removed under reduced pressure. A solution of the orthoamide **23** (750 mg, 1.3 mmol) in THF (15 mL) was added under N₂ to the residue, and the mixture was stirred at 65 °C for 3 h. Water was added and the mixture was extracted twice with CHCl₃. The organic extract was washed twice with water and concentrated under reduced pressure. The residue was dissolved in a minimum amount of CHCl₃ and purified by flash chromatography on silica gel. The product was eluted consecutively with CHCl₃, ethyl acetate, ethyl acetate-methanol (9 : 1). The eluate was evaporated to dryness to yield compound **25**. Yield 537 mg (75 %), colorless solid; m. p. 84–86 °C. – *R*_f = 0.2 (ethyl acetate). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.37 and 7.36 [2d, *J* = 8.7 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.93 and 6.92 [2d, *J* = 8.7 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 6.29 [s, 1H, C(5^{IV})H], 5.65 and 5.64 [2s, 2H, C(3)H and C(8)H], 4.15 [bt, *J* = 13.4 Hz, 2H, C(10)H₂], 4.09 [s, 1H, C(6)H], 3.95–3.88 [m, 2H, C(1)H and C(1^I)H], 3.85 [dd, *J* = 8.4, 1.5 Hz, 1H, C(5)H], 3.75 and 3.74 [2s, 6H, 2ArOCH₃], 3.18 [s, 3H, C(1^I)OCH₃], 2.98 [s, 6H, N(CH₃)₂], 2.92 and 2.91 [dd, *J* = 14.0, 3.0 Hz, 1H, C(2^I)Ha], 2.59 and 2.57 [dd, *J* = 14.0, 8.0 Hz, 1H, C(2^I)Hb], 2.32 (s, 3H, pyrimidine residue CH₃). – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 165.43, 165.33, and 162.00 [C(2^{IV}), C(4^{IV}), and C(6^{IV})], 159.46 and 159.42 [C(4^{II}) and C(4^{III})], 130.99 and 130.74 [C(1^{II}) and C(1^{III})], 127.48 and 127.33 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.42 and 113.30 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.42 [C(5^{IV})], 99.29 [C(3) and C(8)], 79.22 [C(5)], 76.51 [C(1^I)], 69.76 [C(1)], 69.23 [C(10)], 68.80 [C(6)], 58.43 [C(1^I)OCH₃], 55.12 and 55.10 (2 ArOCH₃), 39.70 [C(2^I)], overlapped by the solvent signal, detectable by DEPT-135], 36.51 [N(CH₃)₂], 25.97 [C(2^{IV})CH₃]. – C₃₀H₃₇N₃O₇ (551.66): calcd. C 65.32, H 6.76, N 7.62; found C 64.42, H 6.66, N 6.94. – HRMS ((+)-ESI): *m/z* = 552.2710 (calcd 552.2710 for C₃₀H₃₈N₃O₇, [M+H]⁺).

6-Dimethylamino-4-[(*R*)-methoxy-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]methyl]-2-phenyl-pyrimidine (**26**)

Benzamidine hydrochloride (470 mg, 3 mmol) was added to a solution obtained by addition of Na metal (70 mg, 3 mmol) to ethanol (20 mL). After stirring at r. t. for 30 min, the solvent was removed under reduced pressure. A solution of the orthoamide **22** (791 mg, 1.4 mmol) in THF (16 mL)

was added, and the mixture was stirred for 3 h at 65 °C. Water was added, and the mixture was extracted twice with CHCl₃. The organic extract was washed twice with water and concentrated under reduced pressure. Methanol was added to the red-brownish residue. The product crystallized and was collected by filtration, washed with methanol and dried to yield compound **26**. Yield 586 mg (70 %), yellowish crystals; m. p. 212–214 °C. – *R*_f = 0.44 (CHCl₃-ethyl acetate, 9 : 1). – ¹H NMR (500 MHz, [D₆]DMSO, 323 K): δ = 8.41–8.35 [m, 2H, Ph, C(2)H and C(6)H], 7.46 (m, 3H, Ph, C(3)H, C(4)H, and C(5)H), 7.44 and 7.19 [2d, *J* = 8.8 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.96 and 6.78 [2d, *J* = 8.7 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 6.67 [s, 1H, C(5^{IV})H], 5.71 [s, 1H, C(8)H], 5.56 [s, 1H, C(3)H], 4.51 and 4.50 [dd, *J* = 9.0, 1.5 Hz, C(5)H], 4.39 [d, *J* = 9.0 Hz, 1H, C(1^I)H], 4.27 [s, 1H, C(6)H], 4.22 and 4.18 [2d, *J* = 12.5 Hz, 2H, C(10)H₂], 4.00 [s, 1H, C(1)H], 3.77 and 3.67 [2s, 6H, 2ArOCH₃], 3.30 [s, 3H, C(1^I)OCH₃], 3.14 [s, 6H, N(CH₃)₂]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 164.52 [C(4^{IV})], 162.26 and 161.94 [C(2^{IV}) and C(6^{IV})], 159.30 and 159.24 [C(4^{II}) and C(4^{III})], 138.31 [Ph, C(1)], 130.97 and 130.52 [C(1^{II}) and C(1^{III})], 129.78 [Ph, C(4)], 127.94 and 127.59 [Ph, C(2), C(3), C(5), and C(6)], 127.10 and 127.08 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.28 and 113.05 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 100.23 [C(5^{IV})], 99.17 and 99.03 [C(3) and C(8)], 79.75 [C(1^I)], 77.98 [C(5)], 69.63 [C(1)], 69.20 [C(10)], 68.60 [C(6)], 56.89 [C(1^I)OCH₃], 54.98 and 54.90 (2 ArOCH₃), 36.48 [N(CH₃)₂]. – C₃₄H₃₇N₃O₇ (599.67): calcd. C 68.10, H 6.22, N 7.01; found C 68.14, H 6.21, N 6.87. – HRMS ((+)-ESI): *m/z* = 600.2707 (calcd. 600.2710 for C₃₄H₃₈N₃O₇, [M+H]⁺).

6-Dimethylamino-4-[(2*R*)-2-methoxy-2-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]ethyl]-2-phenyl-pyrimidine (**27**)

Benzamidine hydrochloride (390 mg, 2.5 mmol) was added to a solution obtained by addition of Na metal (60 mg, 2.6 mmol) to ethanol (10 mL). After stirring at r. t. for 30 min, the solvent was removed under reduced pressure. A solution of the orthoamide **23** (713 mg, 1.2 mmol) in THF (14 mL) was added, and the mixture was stirred under N₂ at 65 °C for 3 h. Water was added, and the mixture was extracted twice with CHCl₃. The combined organic extracts were washed twice with water and concentrated under reduced pressure. The residue was dissolved in a minimal amount of CHCl₃ and purified by flash chromatography on silica gel by consecutive elution with CHCl₃, CHCl₃-ethyl acetate (95 : 5), and CHCl₃-ethyl acetate (9 : 1). After the concentration of the eluate under reduced pressure, the residue was recrystallized from ethanol to yield compound **27**. Yield 300 mg (41 %), colorless crystals; m. p. 138–

140 °C. – R_f = 0.36 (CHCl₃-ethyl acetate, 9 : 1). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 8.39–8.33 [m, 2H, Ph, C(2)H and C(6)H], 7.49–7.35 [m, 7H, Ph, C(3)H, C(4)H, C(5)H, and C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.97–6.91 [m, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 6.44 [s, 1H, C(5^{IV})H], 5.66 [s, 2H, C(3)H], C(8)H], 4.2–4.08 [m, 4H, C(1^I)H, C(6)H, C(10)H₂], 3.96–3.87 [m, 2H, C(1)H, C(5)H], 3.74 and 3.73 (2s, 6H, 2 ArOCH₃), 3.27 [s, 3H, C(1^I)OCH₃], 3.09 [bs, 6H, N(CH₃)₂], 3.07 [m, 1H, C(2^I)Ha], 2.80–2.72 [m, 1H, C(2^I)Hb]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 165.56 [C(4^{IV})], 162.19 and 161.45 [C(2^{IV}) and C(6^{IV})], 159.44 and 159.35 [C(4^{II}) and C(4^{III})], 138.42 [Ph, C(1)], 130.94 and 130.65 [C(1^{II}) and C(1^{III})], 129.97 [Ph, C(4)], 128.16 and 127.56 [Ph, C(2), C(3), C(5) C(6)], 127.41 and 127.19 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.36 and 113.31 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 100.58 [C(5^{IV})], 99.39 and 98.99 [C(3) and C(8)], 78.92 [C(1^I)], 76.31 [C(5)], 69.78 [C(1)], 69.19 [C(10)], 68.72 [C(6)], 58.21 [C(1^I)OCH₃], 55.08 and 55.05 [2 ArOCH₃], 39.13 [C(2^I)H₂], overlapped by the solvent signal, detectable by DEPT 135], 36.54 [N(CH₃)₂]. – C₃₅H₃₉N₃O₇ (613.70): calcd. C 68.50, H 6.41, N 6.85; found: C 68.01, H 6.34, N 6.44. – HRMS ((+)-ESI): m/z = 614.2869 (calcd. 614.2866 for C₃₅H₄₀N₃O₇, [M+H]⁺).

6-Dimethylamino-4-[(R)-methoxy-(1S,3S,5R,6R,8R)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]methyl]-2-amino-pyrimidine (28)

Guanidine hydrochloride (285 mg, 3 mmol) was added to a solution obtained by addition of Na metal (70 mg, 3 mmol) to ethanol (20 mL), and the solution was stirred at r. t. under N₂ for 2 h. The solvent was removed under reduced pressure. A solution of the orthoamide **22** (791 mg, 1.4 mmol) in THF (16 mL) was added, and the mixture was stirred at 65 °C under N₂ for 3 h. Water was added, and the mixture was extracted twice with CHCl₃. The organic extract was washed with water, concentrated under reduced pressure, and the residue was purified by flash chromatography on silica gel by consecutive elution with CHCl₃, acetonitrile, acetonitrile-methanol (95 : 5). Compound **28** was obtained after the evaporation of the eluate to dryness under reduced pressure. Yield 330 mg (44%), yellowish solid; m. p. 134–136 °C. – R_f = 0.54 (ethyl acetate-MeOH, 8 : 2). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.41 and 7.23 [2d, J = 8.7 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.97 and 6.87 [2d, J = 8.7 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 6.00 [bs, 3H, C(5^{IV})H and NH₂], 5.68 [s, 1H, C(8)H], 5.52 [s, 1H, C(3)H], 4.30 [dd, J = 9.3, 1.5 Hz, 1H, C(5)H], 4.22–4.05 [m, 4H, C(6)H, C(1^I)H, C(10)H₂], 3.95 [s, 1H, C(1)H], 3.77 and 3.72 (2s, 6H, 2 ArOCH₃), 3.19 [s, 3H, C(1^I)OCH₃], 2.96 (s, 6H, N(CH₃)₂). – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 163.14 [C(6^{IV})], 159.44 and 159.41 [C(4^{II}) and C(4^{III})],

131.12 and 130.66 [C(1^{II}) and C(1^{III})], 127.49 and 127.29 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.42 and 113.28 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.28 and 99.18 [C(3) and C(8)], 92.73 [C(5^{IV})], 79.86 [C(1^I)], 78.04 [C(5)], 69.79 [C(1)], 69.27 [C(10)], 68.62 [C(6)], 56.79 [C(1^I)OCH₃], 55.16 and 55.13 (2 ArOCH₃), 36.62 [N(CH₃)₂]. – C₂₈H₃₄N₄O₇ (538.59): calcd. C 62.44, H 6.36, N 10.40; found C 61.24, H 6.28, N 10.21. – HRMS ((+)-ESI): m/z = 539.2505 (calcd. 539.2505 for C₂₈H₃₅N₄O₇, [M+H]⁺).

6-Dimethylamino-4-[(2R)-2-methoxy-2-[(1S,3S,5R,6R,8R)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]ethyl]-2-amino-pyrimidine (29)

Guanidine hydrochloride (285 mg, 3 mmol) was added to a solution obtained by addition of Na metal (70 mg, 3 mmol) to ethanol (20 mL), and the solution was stirred at r. t. under N₂ for 1 h. The solvent was removed under reduced pressure. A solution of the orthoamide **23** (697 mg, 1.2 mmol) in THF (14 mL) was added, and the mixture was stirred at 65 °C under N₂ for 3 h. Water was added, and the mixture was extracted twice with CHCl₃. The combined organic extracts were washed with water, concentrated under reduced pressure, and the residue was purified by flash chromatography with consecutive elution with ethyl acetate, ethyl acetate-methanol (9 : 1), ethyl acetate-methanol (8 : 2). Compound **29** was obtained after the evaporation of the eluate to dryness under reduced pressure. Yield 310 mg (47%), yellowish solid; m. p. 102–104 °C. – R_f = 0.3 (ethyl acetate-MeOH, 8 : 2). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.37 [d, J = 8.8 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.94 and 6.93 [2d, J = 8.8 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.92 (bs, 2H, NH₂), 5.81 [s, 1H, C(5^{IV})H], 5.65 and 5.64 [2s, 2H, C(3)H and C(8)H], 4.15 [bt, 2H, J = 13.9 Hz, C(10)H₂], 4.09 [s, 1H, C(6)H], 3.98–3.88 [m, 2H, C(1)H and C(1^I)H], 3.80 [d, J = 9 Hz, 1H, C(5)H], 3.75 (s, 6H, 2 ArOCH₃), 3.19 [s, 3H, C(1^I)OCH₃], 2.93 [s, 6H, N(CH₃)₂], 2.78 and 2.77 [dd, J = 14.0, 2.7 Hz, 1H, C(2^I)Ha], 2.41 and 2.39 [dd, J = 14.0, 9.0 Hz, 1H, C(2^I)Hb]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 165.89, 163.26, and 162.40 [C(2^{IV}), C(4^{IV}), and C(6^{IV})], 159.53 [C(4^{II}) and C(4^{III})], 131.04 and 130.80 [C(1^{II}) and C(1^{III})], 127.49 and 127.39 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.45 and 113.32 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.41 and 99.38 [C(3) and C(8)], 92.51 [C(5^{IV})], 79.30 [C(5)], 76.39 [C(1^I)], 69.74 [C(1)], 69.23 [C(10)], 68.71 [C(6)], 58.65 [C(1^I)OCH₃], 55.12 (ArOCH₃), 39.97 [C(2^I)], overlapped by the solvent signal, detectable by DEPT-135], 36.51 [N(CH₃)₂]. – C₂₉H₃₆N₄O₇ (552.62): calcd. C 63.03, H 6.57, N 10.14; found C 61.70, H 6.54, N 9.54. – HRMS ((+)-ESI): m/z = 553.2656 (calcd. 553.2662 for C₂₉H₃₇N₄O₇, [M+H]⁺).

6-Dimethylamino-4-[(*R*)-methoxy-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]methyl]-2-(1-piperidyl)pyrimidine (**30**)

Piperidine-1-carboxamide sulfate (2 g, 5.7 mmol) was added to a solution obtained by addition of Na metal (300 mg, 13 mmol) to ethanol (30 mL). The mixture was stirred for 30 min at r. t., then evaporated to dryness. Acetonitrile (30 mL) was added to the residue, the mixture was stirred for a few minutes and then filtered. The clear filtrate was evaporated to yield piperidine-1-carboxamide base as a colorless solid (1.3 g, 90%). Piperidine-1-carboxamide base (0.9 g, 7 mmol) was added to a solution of the orthoamide **22** (682 mg, 1.2 mmol) in THF (14 mL), and the mixture was stirred at 55 °C under N₂ for 21 h. Water was added, and the mixture was extracted twice with CHCl₃. The combined organic extracts were washed with water and concentrated under reduced pressure. Methanol was added to the residue, and the suspension was heated to reflux. After cooling to r. t. the suspension was filtered. The solid material was washed with methanol and diethyl ether and dried to yield compound **30**. Yield 510 mg (70%), yellowish crystals; m. p. 194–196 °C. – *R*_f = 0.68 (CHCl₃-THF, 1 : 1). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.40 and 7.21 [2d, *J* = 8.7 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.96 and 6.85 [2d, *J* = 8.7 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.97 [s, 1H, C(5^{IV})], 5.67 [s, 1H, C(8)H], 5.51 [s, 1H, C(3)H], 4.33 and 4.32 [dd, *J* = 9.5, 1.5 Hz, C(5)H], 4.19, [s, 1H, C(6)H], 4.18 and 4.14 [dd, 2H, *J* = 12.3, 1.3 Hz, C(10)H₂], 4.09 [d, *J* = 9.5 Hz, 1H, C(1^I)H], 3.95 [s, 1H, C(1)H], 3.76 and 3.71 (2s, 6H, 2 ArOCH₃), 3.67 (bt, *J* = 5.0 Hz, 4H, N-CH₂), 3.22 [s, 3H, C(1^I)OCH₃], 2.96 [s, 6H, N(CH₃)₂], 1.57 [m, 2H, piperidine, γ-CH₂], 1.45 [m, 4H, piperidine, β-CH₂]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 164.88, 162.84, 160.94 [C(2^{IV}), C(6^{IV}), C(4^{IV})], 159.36 and 159.35 [C(4^{II}) and C(4^{III})], 131.03 and 130.65 [C(1^{II}) and C(1^{III})], 127.36 and 127.23 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.37 and 113.17 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.23 and 99.19 [C(3) and C(8)], 91.49 [C(5^{IV})], 79.89 [C(1^I)], 78.07 [C(5)], 69.72 [C(1)], 69.29 [C(10)], 68.69 [C(6)], 56.87 [C(1^I)OCH₃], 55.07 [ArOCH₃], 44.25 (piperidine, N-CH₂), 36.47 [N(CH₃)₂], 25.26 [piperidine, γ-CH₂], 24.52 [piperidine, β-CH₂]. – C₃₃H₄₂N₄O₇ (606.70): calcd. C 65.33, H 6.98, N 9.23; found C 65.58, H 6.96, N 8.96. – HRMS ((+)-ESI): *m/z* = 607.3140 (calcd. 607.3132 for C₃₃H₄₃N₄O₇, [M+H]⁺).

6-Dimethylamino-4-[(2*R*)-2-methoxy-2-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]ethyl]-2-(1-piperidyl)pyrimidine (**31**)

Piperidine-1-carboxamide base (see previous procedure) (380 mg, 3 mmol) was added to a solution of the orthoamide **23** (787 mg, 1.3 mmol) in THF (15 mL), and the

mixture was stirred at 60 °C for 3 h. Water was added and the mixture was extracted twice with CHCl₃. The combined organic extracts were washed with water and concentrated under reduced pressure. The residue was purified by flash chromatography on silica gel by consecutive elution with CHCl₃, CHCl₃-ethyl acetate (1 : 1), ethyl acetate, ethyl acetate-methanol (9 : 1). After concentration of the eluate under reduced pressure, the residue was recrystallized from ethanol to yield compound **31**. Yield 520 mg (62%), yellowish crystals; m. p. 130–134 °C. – *R*_f = 0.36 (ethyl acetate). – ¹H NMR (500 MHz, [D₆]DMSO): δ = 7.36 [d, *J* = 8.8 Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.91 [d, *J* = 8.8 Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.76 [s, 1H, C(5^{IV})], 5.65 [s, 1H, C(8)H], 5.62 [s, 1H, C(3)H], 4.21–3.97 [m, 4H, C(10)H₂, C(6)H, C(1^I)H], 3.95–3.84 [m, 2H, C(1)H, C(5)H], 3.74 [s, 6H, 2 ArOCH₃], 3.66 [bt, *J* = 5.0 Hz, 4H, piperidine, N-CH₂], 3.26 [s, 3H, C(1^I)OCH₃], 2.94 [s, 6H, N(CH₃)₂], 2.85 and 2.84 [dd, *J* = 14.0, 3.0 Hz, 1H, C(2^I)Ha], [C(2^I)Hb is overlapped by the solvent signal at 2.5 ppm], 1.56 [m, 2H, piperidine, γ-CH₂], 1.43 [m, 4H, piperidine, β-CH₂]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): δ = 165.76, 162.82, and 160.63 [C(4^{IV}), C(6^{IV}), and C(2^{IV})], 159.38 and 159.29 [C(4^{II}) and C(4^{III})], 130.96 and 130.66 [C(1^{II}) and C(1^{III})], 127.35 and 127.07 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 113.32 and 113.26 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.34 and 98.89 [C(3) and C(8)], 91.83 [C(5^{IV})], 78.86 [C(5)], 76.00 [C(1^I)], 69.82 [C(1)], 69.19 [C(10)], 68.68 [C(6)], 58.16 [C(1^I)OCH₃], 55.07 and 55.05 (2 ArOCH₃), 44.15 (piperidine, N-CH₂), 39.12 [C(2^I), overlapped by the solvent signal, detectable by DEPT-135], 36.39 [N(CH₃)₂], 25.30 (piperidine, γ-CH₂), 24.55 (piperidine, β-CH₂). – C₃₄H₄₄N₄O₇ (620.73): calcd. C 65.79, H 7.14; found C 64.40, H 6.67. – HRMS ((+)-ESI): *m/z* = 621.3288 (calcd. 621.3288 for C₃₄H₄₅N₄O₇, [M+H]⁺).

5,5-Bis(dimethylamino)-2-cyano-3-[(*R*)-methoxy-[(1*S*,3*S*,5*R*,6*R*,8*R*)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]methyl]-penta-2,4-dienitrile (**32**)

A solution of malononitrile (200 mg, 3 mmol) in THF (3 mL) was added to a THF solution of the orthoamide **22** (22 mL, 631 mg, 1.1 mmol). The color of the mixture turned immediately to deep orange. The mixture was stirred at r. t. for 24 h. The solvent was removed under reduced pressure. The viscous orange-brown oily residue was dissolved in CHCl₃ and separated by flash chromatography on silica gel by consecutive elution with CHCl₃, CHCl₃-THF (9 : 1), CHCl₃-THF-MeOH (70 : 30 : 1.5), and CHCl₃-THF-MeOH (50 : 50 : 1.5) to yield after evaporation of the eluate compound **32**. Yield 500 mg (76%), yellow-orange amorphous solid; m. p. 125–130 °C. – *R*_f = 0.58 (CHCl₃-THF, 1 : 1). – ¹H NMR (500 MHz, [D₆]DMSO, 297 K):

$\delta = 7.41$ and 7.33 [2d, $J = 8.8$ Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.93 and 6.90 [2d, $J = 8.8$ Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.65 [s, 1H, C(8)H], 5.57 [s, 1H, C(3)H], 4.54 [s, 1H, C(3^{IV})H], 4.29 [d, $J = 9.0$ Hz, 1H, C(1^I)H], 4.20 – 4.06 [m, 4H, C(5)H, C(6)H, C(10)H₂], 3.92 [s, 1H, C(1)H], 3.75 and 3.74 [2s, 6H, 2 ArOCH₃], 3.27 [s, 3H, C(1^I)OCH₃], 2.90 [s, 12H, 2 N(CH₃)₂]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): $\delta = 167.47$ and 160.70 [C(4^{IV}) and C(2^{IV})], 159.42 and 159.32 [C(4^{II}) and C(4^{III})], 130.94 and 130.39 [C(1^{II}) and C(1^{III})], 127.44 and 127.24 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 120.32 (CN), 113.30 and 113.20 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.45 [C(3)], 99.02 [C(8)], 89.59 [C(3^{IV})], 79.67 [C(1^I)], 78.93 [C(5)], 69.75 [C(1)], 69.17 [C(10)], 68.27 [C(6)], 56.63 [C(1^I)OCH₃], 55.09 [ArOCH₃], 45.90 [C(1^{IV})], 40.71 [N(CH₃)₂]. – C₃₂H₃₈N₄O₇ (590.66): calcd. C 65.07, H 6.48, N 9.49; found C 64.48, H 6.46, N 9.24. – HRMS ((+)-ESI): $m/z = 591.2804$ (calcd. 591.2819 for C₃₂H₃₉N₄O₇, [M+H]⁺), 613.2634 (calcd. 613.2638 for C₃₂H₃₈N₄O₇Na, [M+Na]⁺), 629.2374 (calcd. 629.2377 for C₃₂H₃₈N₄O₇K, [M+K]⁺).

5,5-Bis(dimethylamino)-2-cyano-3-[(2R)-2-methoxy-2-[(1S,3S,5R,6R,8R)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]ethyl]-penta-2,4-dienitrile (33)

Malononitrile (300 mg, 4.5 mmol) was added to a THF solution of the orthoamide **23** (25 mL, 697 mg, 1.2 mmol). The color of the mixture turned immediately to deep orange. The mixture was stirred at r. t. for 24 h. A 10% aqueous solution of NH₄Cl (50 mL) was added, and the mixture was extracted with ethyl acetate. The organic extract was washed with water and concentrated under reduced pressure. The viscous orange-brown oily residue was dissolved in CHCl₃ and separated by flash chromatography on silica gel by consecutive elution with CHCl₃, CHCl₃-ethyl acetate (1 : 1), ethyl acetate, ethyl acetate-MeOH-triethylamine (9 : 1 : 0.1) to yield after concentration of the eluate the compound **33**. Yield 460 mg (63%), yellow-orange amorphous solid; m. p. 94–100 °C. – $R_f = 0.43$ (ethyl acetate). – ¹H NMR (500 MHz, [D₆]DMSO, 296 K) (mixture of rotamers): $\delta = 7.46$ – 7.30 [m, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.98 – 6.87 [m, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.65 [s, 1.5H, incl. C(8)H and 0.5 C(3)H], 5.63 [s, 0.5H, C(3)H], 4.75 and 4.36 [2s, 2 × 0.5H, C(3^{IV})H], 4.15 [bt, $J = 13.3$ Hz, 2H, C(10)H₂], 4.10 and 4.04 [2s, 2 × 0.5H, C(6)H], 3.92 and 3.91 [2s, 2 × 0.5H, C(1)], 3.84 [d, $J = 8.4$ Hz, 0.5 H, C(5)H], 3.77 – 3.73 [m, 7H, incl. 2 ArOCH₃, 0.5 C(5)H, and 0.5 C(1^I)H], 3.51 – 3.43 [m, 0.5H, C(1^I)H], 3.36 and 3.43 [2s, 2 × 1.5H, C(1^I)OCH₃], 2.91 and 2.70 [2s, 2 × 6H, 2 N(CH₃)₂], 2.78 – 2.72 [m, 1H, C(2^I)H_a], 2.45 – 2.33 [m, 1H, C(2^I)H_b]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): $\delta = 167.35$ and 160.27 [C(4^{IV})], 165.59 and

162.36 [C(2^{IV})], 159.49 and 159.43 [C(4^{II}) and C(4^{III})], 131.05 , 130.94 , 130.66 , and 130.59 [C(1^{II}) and C(1^{III})], 127.61 , 127.55 , 127.31 , and 127.15 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 120.32 and 119.96 (CN), 113.43 , 113.39 , and 113.32 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.39 [C(8)], 99.23 and 98.89 [C(3)], 91.67 and 88.53 [C(3^{IV})], 79.15 and 79.09 [C(5)], 77.96 and 77.84 [C(1^I)], 69.73 and 69.64 [C(1)], 69.26 and 69.15 [C(10)H₂], 68.91 and 68.16 [C(6)], 59.79 and 58.87 [C(1^I)OCH₃], 55.19 and 55.15 [ArOCH₃], 52.18 and 47.51 [C(1^{IV})], 40.95 and 40.68 [N(CH₃)₂], 39.66 (overlapped by the solvent signal, detectable by DEPT-135) and 34.60 [C(2^I)H₂]. – C₃₃H₄₀N₄O₇ (604.69): calcd. C 65.55, H 6.67, N 9.27; found C 64.80, H 6.58, N 8.34. – HRMS ((+)-ESI): $m/z = 605.2930$ (calcd. 605.2975 for C₃₃H₄₁N₄O₇, [M+H]⁺), 627.2750 (calcd. 627.2794 for C₃₃H₄₀N₄O₇Na, [M+Na]⁺), 643.2479 (calcd. 643.2534 for C₃₃H₄₀N₄O₇K, [M+K]⁺).

3-Cyano-6-dimethylamino-4-[(R)-methoxy-[(1S,3S,5R,6R,8R)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl]methyl]-2-oxo-1,2-dihydropyridine (36)

Cyanoacetamide (360 mg, 4.3 mmol) was added under N₂ to a THF solution of the orthoamide **22** (17 mL, 908 mg, 1.6 mmol). The color of the mixture turned immediately to deep orange. The mixture was stirred at r. t. for 24 h, then concentrated under reduced pressure. 2-Propanol (30 mL) was added to the residue, and the mixture was stirred for 2 h at 80 °C. The initial yellow-orange color of the mixture quickly disappeared, and the pale-yellow compound began to crystallize. The suspension was filtered. The crystalline product was washed with 2-propanol and dried to yield compound **36**. Yield 556 mg (62%), pale-yellow crystals; m. p. 222–224 °C. – $R_f = 0.46$ (CHCl₃-THF-MeOH, 10 : 2 : 1). – FT-IR (ATR): $\nu = 2967$, 2908 , 2837 (OCH₃), 2208 (CN), 1599 (C=O), 1514 , 1244 , 1114 , 1030 , 827 , 802 , 776 cm⁻¹. – ¹H NMR (500 MHz, [D₆]DMSO): $\delta = 11.27$ (bs, 1H, NH), 7.41 and 7.29 [2d, $J = 8.7$ Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.94 and 6.87 [2d, $J = 8.7$ Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.87 [bs, 1H, C(5^{IV})H], 5.69 [s, 1H, C(8)H], 5.54 [s, 1H, C(3)H], 4.58 [d, $J = 9$ Hz, C(5)H], 4.25 – 4.08 [m, 4H, C(1^I)H, C(6)H, C(10)H₂], 3.94 [s, 1H, C(1)H], 3.76 and 3.73 [2s, 6H, 2 ArOCH₃], 3.24 [s, 3H, C(1^I)OCH₃], 3.05 [s, 6H, N(CH₃)₂]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): $\delta = 159.41$ and 159.34 [C(4^{II}) and C(4^{III})], 130.89 and 130.40 [C(1^{II}) and C(1^{III})], 127.42 and 127.17 [C(2^{II}), C(6^{II}), C(2^{III}), C(6^{III})], 117.10 (CN), 113.35 and 113.21 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.12 and 99.07 [C(3) and C(8)], 78.72 [C(5)], 77.58 [C(1^I)], 69.66 [C(1)], 69.21 [C(10)], 68.32 [C(6)], 57.17 [C(1^I)OCH₃], 55.09 [ArOCH₃]. – C₃₀H₃₃N₃O₈ (563.59): calcd. C 63.93, H 5.90, N 7.46; found C 62.63, H 5.84, N 7.34. – HRMS ((+)-ESI): $m/z = 564.2344$ (calcd. 564.2345

for $C_{30}H_{34}N_3O_8$, $[M+H]^+$, 586.2152 (calcd. 586.2165 for $C_{30}H_{33}N_3O_8Na$, $[M+Na]^+$), 602.1888 (calcd. 602.1904 for $C_{30}H_{33}N_3O_8K$, $[M+K]^+$).

3-Cyano-6-dimethylamino-4-[(2R)-2-methoxy-2-[(1S,3S,5R,6R,8R)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo-[4.4.0]decan-5-yl]ethyl]-2-oxo-1,2-dihydropyridine (37)

Cyanoacetamide (120 mg, 1.4 mmol) was added under N_2 to a THF solution of the orthoamide **23** (6 mL, 318 mg, 0.54 mmol). The mixture was stirred at r. t. for 24 h, then concentrated under reduced pressure. 2-Propanol (10 mL) was added to the residue, and the mixture was stirred for 2 h at 80 °C. The initial yellow-orange color of the mixture quickly disappeared, and a pale-yellow compound began to crystallize. The suspension was filtered. The crystalline product was washed with 2-propanol and dried to yield compound **37**, which was recrystallized from acetonitrile. Yield 222 mg (70%), pale-yellow crystals; m. p. 238–240 °C. – FT-IR (ATR): $\nu = 3508, 2960, 2922, 2830$ (OCH₃), 2211 (CN), 1613, 1603 (C=O), 1515, 1247, 1231, 1170, 1109, 1083, 1028, 829, 777 cm^{-1} . – ¹H NMR (500 MHz, [D₆]DMSO): $\delta = 11.13$ (bs, 1H, NH), 7.37 and 7.36 [2d, $J = 8.7$ Hz, 4H, C(2^{II})H, C(6^{II})H, C(2^{III})H, C(6^{III})H], 6.92 and 6.91 [2d, $J = 8.7$ Hz, 4H, C(3^{II})H, C(5^{II})H, C(3^{III})H, C(5^{III})H], 5.65 [bs, 3H, C(5^{IV})H, C(3)H, C(8)H], 4.15 [m, 2H, C(10)H₂], 4.10 [s, 1H, C(6)H], 3.94 [s, 1H, C(1)H], 3.85–3.79 [m, 2H, C(5)H + C(1^I)H], 3.75 and 3.74 (2s, 6H, 2 ArOCH₃), 3.31 [s, 3H, C(1^I)OCH₃], 2.99–2.93 [m, 7H, [N(CH₃)₂]_s at 2.95 ppm] and C(2^I)Ha], 2.70 and 2.69 [2d, $J = 13.7, 5.8$ Hz, 1H, C(2^I)Hb]. – ¹³C NMR (125.76 MHz, [D₆]DMSO): $\delta = 159.40$ and 159.34 [C(4^{II}) and C(4^{III})], 130.87 and 130.51 [C(1^{II}) and C(1^{III})], 127.35 and 127.21 [C(2^{II})], C(6^{II}), C(2^{III}), C(6^{III})], 118.01 (CN), 113.36 and 113.25 [C(3^{II}), C(5^{II}), C(3^{III}), C(5^{III})], 99.12 [C(3) and C(8)], 78.49 [C(5)], 76.78 [C(1^I)], 69.68 [C(1)], 69.19 [C(10)], 68.63 [C(6)], 58.80 [C(1^I)OCH₃], 55.09 and 55.06 (2 ArOCH₃). – $C_{31}H_{35}N_3O_8$ (577.62): calcd. C 64.46, H 6.11, N 7.27; found C 62.02, H 5.91, N 6.84. – HRMS ((+)-ESI): $m/z = 600.2320$ (calcd. 600.2321 for $C_{31}H_{35}N_3O_8Na$, $[M+Na]^+$).

(2S,3R,4S,5R)-5-(3-Cyano-6-dimethylamino-2-oxo-1,2-dihydropyridin-4-yl)-2,3,4-trihydroxy-5-methoxypentan-1-ol (38)

Compound **36** (250 mg, 0.44 mmol) was dissolved in a mixture of ethanol (5 mL) and 37% aqueous HCl (0.2 mL). After 48 h at r. t., the mixture was diluted with water (5 mL) and extracted three times with CH₂Cl₂ (10 mL). The aqueous phase was concentrated under reduced pressure. The

residue was dissolved in 5 mL ethanol and the solution filtered. The clear filtrate was concentrated under reduced pressure. Acetone (ca. 5 mL) was added to the residue. The crystalline material was isolated by filtration, washed several times with acetone and dried to yield compound **38**. Yield 70 mg (48%), pale-yellow crystals; m. p. >280 °C (dec.). – $R_f = 0.58$ (CHCl₃-MeOH, 1 : 1). – FT-IR (ATR): $\nu = 3118$ (OH assoc.), 2984, 2803, 2205 (CN), 1609 (C=O), 1381, 1096 cm^{-1} . – ¹H NMR (500 MHz, D₂O/DSS): $\delta = 5.97$ [s, 1H, C(5^I)H], 4.41 [d, $J = 8.5$ Hz, 1H, C(5)H], 3.96–3.81 [m, 3H, C(2)H, C(3)H, C(4)H], 3.78–3.70 [m, 1H, C(1)Ha], 3.68–3.57 [m, 1H, C(1)Hb], 3.35 [s, 3H, OCH₃], 3.20 [s, 6H, N(CH₃)₂]. – ¹³C NMR (125.76 MHz, D₂O/DSS): $\delta = 167.70$ (C=O), 161.32 [C(4^I)], 156.41 [C(6^I)], 121.63 [CN], 95.54 [C(5^I)], 84.64 [C(5)], 83.79 [C(3^I)], 75.76, 75.17, 72.52 [C(2), C(3), and C(4)], 65.22 [C(1)H₂], 59.88 [OCH₃], 41.73 [N(CH₃)₂]. – HRMS ((+)-ESI): $m/z = 328.1511$ (calcd. 328.1509 for $C_{14}H_{22}N_3O_6$, $[M+H]^+$).

(2S,3R,4S,5R)-6-(3-Cyano-6-dimethylamino-2-oxo-1,2-dihydropyridin-4-yl)-2,3,4-trihydroxy-5-methoxyhexan-1-ol (39)

Compound **37** (340 mg, 1 mmol) was dissolved in a mixture of ethanol (10 mL) and 37% aqueous HCl (0.5 mL). After 48 h at r. t., the mixture was diluted with water (10 mL) and extracted three times with CH₂Cl₂ (15 mL). The aqueous phase was concentrated under reduced pressure. The residue was dissolved in 5 mL ethanol and the solution filtered. The clear filtrate was concentrated under reduced pressure. The residue was dissolved in hot 2-propanol (5 mL). After cooling to r. t., the precipitated product was isolated by filtration, washed with 2-propanol and dried to yield compound **39**. Yield 55 mg (27%), yellowish amorphous solid; m. p. 238 °C (dec.). – $R_f = 0.39$ (CHCl₃-MeOH, 7 : 3). – FT-IR (ATR): $\nu = 3333$ (OH assoc.), 2933, 2201 (CN), 1592 (C=O), 1382, 1066, 996 cm^{-1} . – ¹H NMR (500 MHz, D₂O/DSS): $\delta = 5.84$ [s, 1H, C(5^I)H], 3.88–3.80 [m, 1H, C(3)H], 3.80–3.68 [m, 4H, C(1)Ha, C(2)H, C(4)H, C(5)H], 3.64 and 3.63 [2d, $J = 12.0, 6.8$ Hz, C(1)Hb], 3.34 [s, 3H, C(5)OCH₃], 3.17 [bs, 6H, N(CH₃)₂], 2.99 and 2.98 [2d, $J = 13.8, 3.0$ Hz; 1H, C(6)Ha], 2.74 and 2.73 [2d, $J = 13.8, 8.0$ Hz, 1H, C(6)Hb]. – ¹³C NMR (125.76 MHz, D₂O/DSS): $\delta = 167.25$ (C=O), 161.64 [C(4^I)], 155.83 [C(6^I)], 121.85 (CN), 97.20 [C(5^I)], 85.56 [C(3^I)], 83.53 [C(5)], 75.54 [C(3)], 74.67 and 72.63 [C(2) and C(4)], 65.36 [C(1)], 61.37 [OCH₃], 41.67 [N(CH₃)₂], 39.08 [C(6)]. – HRMS ((+)-ESI): $m/z = 364.1474$ (calcd. 364.1484 for $C_{15}H_{23}N_3O_6Na$, $[M+Na]^+$).

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