
Konstantin Drandarov and Willi Kantlehner

a Institut für Organische Chemie, Universität Stuttgart, Pfaffenwaldring 55, D-70569 Stuttgart, Germany
b Fakultät Chemie/Organische Chemie, Hochschule für Technik und Wirtschaft, Beethovenstr. 1, D-73430 Aalen, Germany

Reprint requests to Prof. Dr. Willi Kantlehner. Fax: +49(7361)5762250. E-mail: willi.kantlehner@htw-aalen.de

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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″-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
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 propargylation [30–32] of protected aldoses or ketoses led to the idea that sugar-derived alkyne carboxylic 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, Mel, 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.]

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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 \( ^{1} \text{S}-\text{epimer} \, 14 \) (27% isol.) crystallized almost quantitatively. The major \( ^{1} \text{R}-\text{epimer} \, 15 \) 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-nitrobenzoyl-Zn dust in DMF-diethyl ether (1 : 1) mixture, analogously to a described procedure [30 – 32], the 4-nitrobenzoyl-methoxybenzylidene-protected 13 was converted to the homoalkynol 16 in 84% yield. The reaction showed excellent diastereoselectivity, and the \( ^{1} \text{R}-\text{epimer} \) was practically the sole product.

Stereochemical assignment

Similar to \( \text{cis-decalin} \), the unsubstituted \( \text{cis-2,4,7,9-tetraoxabicyclo[4.4.0]decane} \) 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, \( R = \text{H} \), Scheme 2, highlighted in rectangle). Earlier studies demonstrated that the “O-inside” conformer 12a (\( R = \text{H} \)) is thermodynamically favored [37]. An equatorial substitution at C(5) in 12a (\( R \neq \text{H} \)) would restrict additionally the ring inversion 12a → 12b due to steric repulsion between the axial substituents in 12b (\( R \neq \text{H} \)). All compounds in the present study are 3,5,8-trisubstituted \( \text{cis-2,4,7,9-tetraoxabicyclo[4.4.0]decane} \) 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(1) 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)-\( \text{cis-2,4,7,9-tetraoxabicyclo[4.4.0]decane} \) derivatives, were particularly useful key spectral features for the identification of the \( ^{1} \text{H} \) and \( ^{13} \text{C} \) NMR signals of the studied compounds. In the \( ^{1} \text{H} \) 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 \( ^{1} \text{H} \) NMR spectra of compounds 17, 18 and 19 show a C(5)H–C(1)H vicinal coupling constant (\( J_{\text{HH}} \)) 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(1) would diverge around the C(5)–C(1) bond axis eclipsing the benzylidene groups at C(3) and C(8). In the \( ^{1} \text{R}-\text{epimer} \, 18 \) 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 \( ^{1} \text{S}-\text{epimer} \, 17 \) 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 \( ^{1} \text{H} \) NMR spectra of compounds 17, 18 and 19, including the most indicative benzylidene C(3)H, C(8)H and C(1)H signals. The C(3)H (\( \delta = 5.80 \) 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 \( ^{1} \text{R}-\text{configuration} \).

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(1) as compound 18 and together with its precursor 16 also has \( ^{1} \text{R}-\text{configuration} \). The presence of a methylene linker at C(1) 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 $^1$H 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 1⁵-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) hexamethyldiguanidinium 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 alkynecarbonyl chloride 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 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 malononitrile in THF for 24 h at r.t. yielded the intensively yellow-orange ketene aminals 32 and 33 in good yields.

In the ambient-temperature (297 K) ¹H NMR spectrum of compound 32, with a ketene aminal functionality directly attached to C(1⁵), 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(4⁵). Additionally, there is evidence for long range correlations between C(1⁵)H and the butadiene quaternary C(1⁴V) and between C(3⁴V)H and C(1⁴V). These spectral data indicate that the nucleophilic attack of the malononitrile takes place on the β-C atom of the orthoamide 22 with the exclusive formation of the ketene aminal 32 (similar to 4a in Scheme 1), and that at ambient temperature there is facile rotation around the C(3⁴V)–C(4⁵) bond of the butadiene residue, which is explicable by the fact that in the “push-pull” ketene aminals 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(1⁵) in this compound keeps the plane of the attached ketene aminal moiety nearly parallel to the C(1⁵)-OMe bond axis, which apparently strongly restricts the free rotation around the C(2⁵)–C(2⁴V) bond at ambient temperature. Here again, the long range correlation between both NMe₂ groups with carbon atom C(4⁵) confirms the ketene aminal structure of compound 33.

The addition of cyanoacetamide to the THF solutions of orthoamides 22 and 23 at r.t. causes instantaneous deep yellow-orange colorization of the mixtures. Presumably this is a result of the rapid formation of the ketene aminals 34 and 35, respectively. However, in both cases the TLC analyses of the reaction mixtures showed, beside the intensively yellow ketene aminal 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 aminal decreased at the expense of a constantly increasing concentration of the colorless products. Due to their spontaneous transformation, the isolation of the initial ketene aminals 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 °C → r.t., 2) hexamethylguanidinium chloride (2), 7 d, r.t.; (b) R(=NH)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 3,5,8-trisubstituted cis-2,4,7,9-tetraoxabicyclo[4.4.0]decane-derived binary conjugates presented here, the conjunctive C atom is labelled as C(1). However, in compounds 25, 27, 29, 31, 33, and 37, this atom is part of a conjunctive ethyl chain and according to the IUPAC nomenclature should be correctly numbered as C(2). The correct IUPAC names of these compounds are given with the corresponding procedures in the Experimental Section.
in both compounds 36 and 37 displaying C(5\(^IV\))H (at δ = 5.87 and 5.65 ppm, respectively), NH (at 11.27 and 11.13 ppm, respect.), and NMe\(_2\) (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 \(^{13}\)C 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 NMe\(_2\) signals were overlapped by the solvent ([D\(_6\)]DMSO) signal. According to consulted NMR experts, the problem was attributed to a cross-relaxation phenomenon. However, the registration of the \(^{13}\)C 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-xylene derivative 38 and the 6-deoxy-D-sorbitol derivative 39, respectively. Fortunately, the \(^{13}\)C 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 in the case of compound 38 and between C(6)H\(_2\) and C(5)I\(_2\) 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 nuclophilic attack from the cyanoacetamide acidic CH\(_2\) 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 NH\(_2\) 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 alkyne carboxylic 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 1-xylene 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 \(^1\)H and at 62.9 MHz for \(^{13}\)C) or Bruker ARX 500 (operating at 500.1 MHz for \(^1\)H and 125.7 MHz for \(^{13}\)C) instruments. The spectra were calibrated using the solvent signal according to [41] or TMS as internal standard unless stated otherwise. For the assignment of \(^1\)H and \(^{13}\)C NMR signals, DEPT and two-dimensional \(^1\)H,\(^1\)H-COSY, \(^1\)H,\(^{13}\)C correlation spectra (HSQC and HMBC) were recorded. Analytical thin-layer chromatography (TLC) was performed on pre-coated POLYGRAM\textsuperscript{\textregistered} SIL G/UV\textsubscript{254} plastic sheets (Machery-Nagel), detection by UV light. Column chromatography was carried out on silica gel 60 (0.063–0.20 mm), Macherey-Nagel. Melting points were determined with a Büchi 510 apparatus (Büchi Laboratoriumschnitt G, 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 microOTOF-Q (Bruker Daltonics) instrument. Solvents and liquid reagents were purified and dried according to recommended procedures.

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

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 K\(_2\)CO\(_3\).
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]). – Rf = 0.5 (CHCl3-dioxane, 1 : 1). – FT-IR (ATR): ν = 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): δ = 7.39 and 7.37 [2d, J = 8.5 Hz, 4H, C(5)H], 6.92 [d, J = 8.6 Hz, 4H, C(3)H], 5.91 [s, 2H, C(3)H and C(5)H]. 4.82 [d, J = 5.4 Hz, 1H, C(1)H]. 4.41 (t, J = 5.6 Hz, 1H, C(2)H), 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)H and 2 ArOCH₃ as s at 3.75 ppm], 3.64–3.52 [m, 1H, C(2)H], 3.48–3.37 [m, 1H, C(2)H]. – 13C NMR (62.89 MHz, [D₆]DMSO): δ = 159.19, 159.32 [C(4)H] and C(4)H, 131.16, 130.90 [C(11)H and C(13)H], 127.47, 127.43 [C(2)H, C(6)H, C(3)H], 113.25, 113.19 [C(3)H], 89.69 [C(2)H], 69.43 [C(10)H], 68.27 [C(6)H], 57.67 [C(1)H], 56.58 [C(2)H], 55.08 (OCH₂)]. – C₂₂H₂₂O₇ (381.39): calcd: C 63.15, H 6.26; found: C 63.04, H 6.21.

(1S,3S,5S,6R,8R)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxacycloc[4.4.0]dec-5-yl-1-hydroxy-prop-2-ynyl (14) and (1R)-1-{(1S,3S,5S,6R,8R)-3,8-Bis(4-methoxyphenyl)-2,4,7,9-tetraoxacycloc[4.4.0]dec-5-yl-1-hydroxy-prop-2-ynyl (15)

A 0.6 M toluene/THF solution of ethinylmagnesium 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 NH₂Cl (1 L). The precipitated material was isolated by filtration, washed with water and air-dried. The resulting slightly yellow 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 withtoluene and dried to yield the pure compound 15.


An 80% toluene solution of propargyl bromide (11.8 mL, 9.44 g, 40 mmol) was added to a suspension of 13 Cl(II) 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 initiated 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. – Rf = 0.45 (CHCl3–TFE, 10:1). – 1H NMR (500 MHz, D6DMSO): δ = 7.39 and 7.38 [2d, J = 8.6 Hz, 4H, C(2)II]H, C(6)II]H, C(6)III]H, C(6)IV]H]; 6.92 [2d, J = 8.8 Hz, 4H, C(3)II]H, C(5)II]H, C(5)III]H, C(5)IV]H]; 5.60 [bs, 2H, C(3)III]H and C(8)II]H]; 5.28 [dd, J = 6.0 Hz, 1H, OH]; 4.19–4.09 [m, 3H, C(6)H + C(10)H2] and 3.92–3.84 [m, 2H, C(1)H, C(1)II]H]; 3.79–3.69 [m, 7H, C(5)H] and 2 ArOC3H7 (at 3.75 ppm)]. – 2.73 (bt, J = 2.5 Hz, 1H, C(3)H); 2.46 [dt, J = 17.0, 2.7 Hz, 1H, C(2)II]H]; 2.30 and 2.28 [2dd, J = 17.0, 2.6 Hz, 1H, C(2)II]H]. – 13C NMR (125.76 MHz, D6DMSO): δ = 159.42 and 159.35 [C(2)II] and C(3)II]; 131.08 and 130.74 [C(1)II] and C(3)II]. 127.43 and 127.41 [C(2)II], C(6)II], C(3)II], C(5)II]; 113.31 and 113.22 [C(3)III], C(5)III], C(3)III]), 99.33 and 99.28 [C(3) and C(8)]; 82.08 [C(3)]; 79.43 [C(5)]; 72.03 [C(4)]; 69.82 [C(1)]; 69.19 [C(10)]; 68.10 [C(6)]; 64.90 [C(1)]; 55.10 and 55.08 (2 ArOC3H7); 23.36 [C(2)]; – C2H5SO2 (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-tetraazabicyclo[4.4.0]deca-5-yl]-1-hydroxybut-3-ene (16)

4-Nitrobenzoyl chloride (250 mg, 1.35 mmol) was added to a mixture of the alkyl 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. – Rf = 0.43 (CHCl3–TFE, 10:2). – FT-IR (ATR): ν = 3269 (C=OH), 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, D6DMSO): ν = 8.35 (d, J = 8.8 Hz, 2H, 4-NO2–Ph, m-H); 8.17 (d, J = 8.8 Hz, 2H, 4-NO2–Ph, a-H); 7.34 and 7.30 [2d, J = 8.8 Hz, 4H, C(3)II]H, C(6)II]H, C(6)III]H, C(6)IV]H]; 6.93 and 6.87 [2d, J = 8.8 Hz, 4H, C(3)III]H, C(5)II]H, and C(5)III]H, C(5)IV]H]; 5.85 and 5.84 [dd, J = 8.2 Hz, 1H, C(1)II]H]; 5.72 [s, 1H, C(3)III], 5.65 [s, 1H, C(5)III], 4.51 and 4.50 [dd, J = 8.9, 1.9 Hz, 1H, C(5)III], 4.33 [bs, 1H, C(6)III], 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(6)OH]; 3.75 and 3.70 (2s, 6H, 2 ArOC3H7). – 13C NMR (125.76 MHz, D6DMSO): δ = 163.39 (C=O), 159.49 (C(4)II] and C(4)III], 150.47 [4-NO2–Ph, C(4)]; 151.34 [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(3)II]; 127.33 and 127.20 [C(2)II], C(6)II]H, C(6)III]H, C(6)IV]H]; 124.05 [4-NO2–Ph, C(3) and C(5)]; 113.41 and 113.28 [C(3)III], C(3)III], C(3)III], 99.31 (C=O), 98.98 [C(3)]; 79.19 [C(2)]; 77.53 [C(5)]; 76.78 [C(3)]; 69.18 [C(1)]; 69.00 [C(6)]; 68.96 [C(10)]; 64.33 [C(1)]; 55.07 (ArOC3H7). – C30H27NO10 (561.53); calcd. C 64.17, H 4.85, N 2.49; found C 64.05, H 4.86, N 2.42.

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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 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; – R₉ = 0.43 (CHCl₃/THF, 1:0.2), – FT-IR (ATR): ν = 3294 (C=CH), 2890, 2834 (OCH₃), 1727 (C=O), 1613 and 1586 (Ar), 1530 and 1518 (Ar and NO₂), 1505 and 1489 (C(15)H, C(3)H and C(5)H), 1451 and 1435 (C(3)H, C(5)H), 1347 and 1328 (C(2)H), 1293 and 1273 (C(5)H, C(3)H, C(5)H), 1278 and 1266 (C(4)H, C(6)H), 1191 and 1173 (C(15)H, C(3)H, C(5)H), 1138 and 1123 (C(3)H, C(3)H, C(5)H), 99.30 [C(3)], 98.81 [C(8)], 79.30 [C(3)], 76.37 [C(5)], 73.26 [C(4)], 69.30 [C(1)], 69.05 [C(1)], 68.88 [C(10)], 68.04 [C(6)], 55.04 and 54.99 (2 ArOCH₃), 20.20 [C(2)] – C₄H₉NO₂ (575.56); calc’d. C 64.69, H(5.08), N 2.43; found C 62.61, H(5.08), N 2.37.

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(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-ylene-1-y1 4-nitrobenzoate (18)

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 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 toluene. Yield 490 mg (72%), slightly pink fine needles; m. p. 196–198 °C; – R₉ = 0.58 (CHCl₃/THF, 10:0.2), – FT-IR (ATR): ν = 3271 (C=CH₂), 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, – ²H 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], 7.74 and 7.27 [2d, J = 8.8 Hz, 4H, C(2)H, C(6)H, C(3)H, and C(5)H], 6.94 and 6.91 [2d, J = 8.8 Hz, 4H, C(3)H, C(5)H, and C(3)H], 5.74 [7s, 1H, C(3)], 5.51 [1H, C(6)], 5.47–5.42 [m, 1H, C(1)], 4.42 and 4.41 [dd, J = 8.8, 1.7 Hz, C(5)H], 4.16 [1H, C(6)H], 4.14 [bs, 2H, C(10)H], 4.02 [1H, C(1)H], 3.76 and 3.75 [2s, 6H, 2 ArOCH₃], 3.69 [d, J = 2.0 Hz, C(6)H], – ²C NMR (125.76 MHz, [D₆]DMSO): δ = 163.08 (C=O), 154.79 and 152.43 (C(4)H and C(1)H), 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(2)H], 127.38 and 126.94 (C(2)H), 126.08 (C(2)H), 125.32 (4-NO₂-Ph, C(3) and C(5)), 113.30 and 113.18 (C(3)₂H), C(3)H, and C(5)H, 99.30 [C(3)], 98.81 [C(8)], 79.30 [C(3)], 76.37 [C(5)], 73.26 [C(4)], 69.30 [C(1)], 69.05 [C(1)], 68.88 [C(10)], 68.04 [C(6)], 55.04 and 54.99 (2 ArOCH₃), 20.20 [C(2)] – C₄H₉NO₂ (575.56); calc’d. 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-prop-2-ylene-1-y1 4-nitrobenzoate (18)

NaH (60% paraffin suspension, 1.85 g, 11.1 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 Mel (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; – R₉ = 0.65 (CHCl₃/THF, 10:0.2), – ²H NMR (500 MHz, [D₆]DMSO): δ = 7.38 and 7.36 [2d, J = 8.6 Hz, 4H, C(2)H, C(6)H, C(3)H, C(5)H], 6.94 and 6.93 [2d, J = 8.9 Hz, 4H, C(3)H, C(5)H, C(3)H, and C(5)H], 5.69 [1H, C(3)H, 5.62 [1H, C(3)H, 4.20 and 4.19 [dd, J = 9.5, 2.0 Hz, 1H, C(1)H], 4.13 [2H, 2H, J = 15 Hz, C(10)H₂], 4.07–4.02 [m, 2H, C(5)H and C(6)H], 3.92 [1H, C(1)H], 3.75 (6s, C(6)H), 3.62 [d, J = 2.0 Hz, 1H, C=CH₂], 3.55 [2s, 3H, C(1)OCH₃] – ²C NMR (125.76 MHz, [D₆]DMSO): δ =
and dried to yield compound. The product was washed with water and methanol to give 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. – R1 = 0.29 (CHC3-THF, 10:1). – 1H NMR (500 MHz, [D6]DMSO): δ = 7.36 [d, J = 8.7 Hz, 4H, C(2)H], C(6)H, C(2)H, C(6)H], 6.92 and 6.93 [2d, J = 8.7 Hz, 4H, C(3)H], C(5)H, C(3)H, C(5)H], C(3)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)H], 3.37 [s, 3H, C(1)OCH3], 2.78 (bt, J = 2.6 Hz, 1H, C=CH), 2.64 [dh, J = 17.0, 2.9 Hz, 1H, C(2)H], 2.31 and 2.30 [2d, J = 17.0, 2.7 Hz, 1H, C(2)Hb]. – 13C NMR (125.76 MHz, [D6]DMSO): δ = 159.36 and 159.26 [C(4)H], C(4)H], 130.84 and 130.48 [C(3)H] and C(3)H], 127.30 and 127.10 [C(2)H], C(6)H], C(2)H], C(6)H], 113.28 and 113.24 [C(3)H], C(5)H], C(3)H], C(5)H], 92.27 [C(3)], 98.99 [C(8)], 81.10 [C(1)H], 77.48 [C(5)H], 74.80 [C(1)H], 72.16 [C(4)H], 69.55 [C(1)], 69.05 [C(10)], 68.21 [C(6)], 57.76 [C(1)OCH3], 55.02 and 54.98 (2 ArOCH3), 19.42 [C(2)H]. – C29H38O7 (440.48): calcd. C 68.17, H 6.41; found C 67.50, H 6.36.

Preparation of THF solutions of (1R)-1-[(1S,3S,5R,6R,8R)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxacyclo[4.4.0]-dec-5-yl]-1-methoxy-4,4,4-tris(dimethylamino)but-2-ynyl (22) and (1R)-1-[(1S,3S,5R,6R,8R)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxacyclo[4.4.0]-dec-5-yl]-1-methoxy-5,5,5-tris(dimethylamino)pent-3-ynyl (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 alkynie 20 (10 g, 23 mmol) or alkynie 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-[(1S,3S,5R,6R,8R)-3,8-bis(4-methoxyphenyl)-2,4,7,9-tetraoxacyclo[4.4.0]-dec-5-yl]methyl]-2-methyl-pyrindine (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 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. – R1 = 0.24 (ethyl acetate). – 1H NMR (500 MHz, [D6]DMSO): δ = 7.41 and 7.18 [2d, J = 8.8 Hz, 4H, C(2)H], C(6)H], C(2)H], C(6)H], 6.96 and 6.84 [2d, J = 8.7 Hz, 4H, C(3)H], C(5)H], C(3)H], C(5)H], 5.62 [s, 1H, C(5)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, 1H, C(5)H], 4.23 [d, J = 9.25 Hz, C(1)H], 4.20 [s, 1H, C(6)H], 4.19–4.12 [2H, C(10)H], 3.96 [s, 1H, C(1)H], 3.76 and 3.70 [2s, 6H, 2ArCH3], 3.18 [s, 3H, C(1)OCH3], 3.00 [s, 6H, N(CH3)2], 2.36 [s, 3H, C(2)H], – 13C NMR (125.76 MHz, [D6]DMSO): δ = 165.84 [C(1)H], 164.08 [C(4)H], 162.12 [C(4)H], 159.36 [C(4)H] and C(4)H], 131.03 and 130.55 [C(1)H] and C(1)H)], 127.33 and 127.25 [C(2)H], C(6)H], C(2)H], C(6)H], 113.35 and 113.20 [C(3)H], C(5)H], C(3)H], C(5)H], 99.59 [C(5)H], 99.15 and 99.10 [C(3) and C(8)], 79.72 [C(1)H], 77.89 [C(5)], 69.67 [C(1)], 69.23 [C(10)], 68.58 [C(6)], 56.87 [C(1)OCH3], 55.08 and 55.05 (2 ArOCH3), 36.55 (N(CH3)2), 25.95 [C(2)H]CH3). – C29H38N2O7 (537.60): calcd. C 64.79, H 6.56, N 7.82; found C 64.57, H 6.58, N 7.63. – HRMS (+)ESI: m/z = 538.2552 (calcd. 538.2553 for C29H38N2O7 [M+H]+).
Acetamide 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. – \( \Delta T = 0.2 \) (ethyl acetate). – \(^1\)H NMR (500 MHz, \( \text{D}_2\text{OJMDO})\): \( \delta = 3.73 \) and 3.76 [2d, \( J = 8.7 \) Hz, 4H, C(2)\( ^\text{III} \)H], 3.82, 3.83 [2d, \( J = 8.7 \) Hz, 4H, C(6)\( ^\text{III} \)H], 6.93 and 6.92 [2d, \( J = 8.7 \) Hz, 4H, C(3)\( ^\text{III} \)H], 6.97, 6.98, 7.02, 7.03 [2m, 1H, C(5)\( ^\text{III} \)H], 7.04, 7.05 [2d, \( J = 8 \) Hz, 2H, C(1)\( ^\text{III} \)H], 7.07, 7.08 [2d, \( J = 8 \) Hz, 2H, C(8)\( ^\text{III} \)H], 7.12, 7.13 [2d, \( J = 8 \) Hz, 2H, C(10)\( ^\text{III} \)H], 7.15, 7.16 [2d, \( J = 8 \) Hz, 2H, C(9)\( ^\text{III} \)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-phenyl-pyrimidine (26)

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 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. – \( \Delta T = 0.44 \) (CHCl3-ethyl acetate, 9:1). – \(^1\)H NMR (500 MHz, \( \text{D}_2\text{OJMDO})\): \( \delta = 8.41–8.35 \) [5m, 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)\( ^\text{III} \)H], C(6)\( ^\text{III} \)H], C(3)\( ^\text{III} \)H], C(6)\( ^\text{III} \)H], 6.96 and 6.72 [2d, \( J = 8.7 \) Hz, 4H, C(3)\( ^\text{III} \)H], C(5)\( ^\text{III} \)H], C(3)\( ^\text{III} \)H], C(5)\( ^\text{III} \)H], 6.67 [1H, C(5)\( ^\text{V} \)H], 5.71 [1H, C(8)H], 5.56 [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)\( ^\text{III} \)H], 4.27 [1H, C(6)H], 4.22 and 4.18 [2d, \( J = 12.5 \) Hz, 2H, C(10)\( ^\text{III} \)H], 4.00 [1H, C(1)\( ^\text{V} \)H], 3.77 and 3.67 [2s, 6H, 2ArOC], 3.30 [3H, C(1)\( ^\text{III} \)OCH\( _3 \)], 3.14 [3H, 6H, N(CH\( _3 \))\( _2 \)]. – \(^{13}\)C NMR (125.76 MHz, \( \text{D}_2\text{OJMDO})\): \( \delta = 164.52 \) [C(4)\( ^\text{IV} \)], 162.26 and 161.94 [C(2)\( ^\text{IV} \) and C(6)\( ^\text{IV} \)], 159.30 and 159.24 [C(4)\( ^\text{III} \) and C(4)\( ^\text{IV} \)], 138.31 [Ph, C(1)], 130.97 and 130.52 [C(1)\( ^\text{III} \) and C(1)\( ^\text{IV} \)], 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)\( ^\text{II} \), C(6)\( ^\text{II} \), C(2)\( ^\text{III} \), C(6)\( ^\text{III} \), 113.28 and 113.05 [C(3)\( ^\text{III} \), C(5)\( ^\text{III} \)], 100.23 [C(5)\( ^\text{V} \)], 99.17 and 99.03 [C(3) and C(8)], 79.75 [C(1)\( ^\text{III} \)], 77.98 [C(5)], 69.63 [C(1)], 69.20 [C(10)], 68.60 [C(6)], 56.89 [C(1)\( ^\text{III} \)OCH\( _3 \)], 54.98 and 54.90 (2 ArOCH\( _3 \)), 36.48 [N(CH\( _3 \))\( _2 \)], – C\( _8\)H\( _7\)N\( _2\)O\( _4\) (599.67): calc. C 56.82, H 6.22, N 7.01; found C 64.18, H 6.21, N 6.87. – HRMS (\(+\)-ESI): \( m/z = 600.2707 \) (calcd. 600.2710 for C\( _{34}\)H\( _{38}\)N\( _7\)O\( _7\), [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-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. – Rf = 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(10)H], C(11)H, C(12)H, C(13)H, C(14)H, 6.97–6.91 [m, 4H, C(3)H], C(5)H, C(7)H, C(9)H, C(15)H, 6.64 [s, 1H, C(5)H3], 5.66 [s, 2H, C(3)H], C(8)H], 4.2–4.08 [m, 4H, C(1)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 ArOC], 3.07 [m, 1H, C(2)H3], 2.80–2.72 [m, 1H, C(2)H)], – 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)I and C(1)II], 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(10)HIII], 113.36 and 113.31 [C(3)III, C(5)III, C(11)HIII], 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)II], 69.19 [C(10)], 68.72 [C(6)], 58.21 [C(10)OCH3]. 55.08 and 55.05 [2 ArOCH3], 39.13 [C(2)H2], overlapped by the solvent signal, detectable by DEPT [135], 36.54 [N(CH3)2], 1.33–2.25 NaOCH3 (613.70); calc. C 68.50, H 6.41, N 6.85; found: C 68.01, H 6.34, N 6.44. – HRMS (+I-ESI): m/z = 614.2869 (calcld. 614.2866 for C35H40N2O7, [M+H]+).

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

Guainidine 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 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 ethyl acetate, ethyl acetate-methanol (50:50), ethyl acetate-MeOH, (95:5), and ethyl acetate-MeOH (5:95). Compound 28 was obtained after the evaporation of the eluate to dryness under reduced pressure. Yield 310 mg (47%), yellowish solid; m.p. 102–104 °C. – Rf = 0.3 (ethyl acetate-MeOH, 8:2). – 1H NMR (500 MHz, [D6]DMSO): δ = 7.37 [d, J = 8.8 Hz, 4H, C(2)H, C(6)H, C(11)H], C(15)H, 6.94 and 6.93 [2d, J = 8.8 Hz, 4H, C(4)H, C(8)H, C(15)H, C(16)H, C(17)H], 5.92 (bs, 2H, NH2), 5.81 [s, 1H, C(3)IV], 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(10)H], 3.80 [d, J = 9 Hz, 1H, C(5)H], 3.75 [s, 6H, 2 ArOCH3], 3.19 [s, 3H, C(1)OCH3], 2.93 [s, 6H, N(CH3)2], 2.78 and 2.77 [dd, J = 14.0, 2.7 Hz, 1H, C(2)H2], 2.41 and 2.39 [dd, J = 14.0, 9.0 Hz, 1H, C(2)H2], – 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], 159.63 [C(4)II and C(4)III], 131.04 and 130.80 [C(1)I and C(1)II], 127.49 and 127.39 [C(1)II and C(1)III], 114.45 and 113.32 [C(3)III, C(5)III, C(7)III, C(9)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)II], 69.23 [C(10)], 68.71 [C(6)], 58.65 [C(1)OCH3], 55.12 [ArOCH3]. 39.97 [C(2)], overlapped by the solvent signal, detectable by DEPT-135, 36.51 [N(CH3)2], 1.26 NaOCH3 (552.62); calcld. C 63.03, H 6.57, N 10.14; found C 61.70, H 6.54, N 9.54. – HRMS (+I-ESI): m/z = 553.2656 (calcld. 553.2662 for C32H37N4O7, [M+H]+).
Piperidine-1-carboxamidine sulfate (2 g, 5 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-carboxamidine base as a colorless solid (1.3 g, 90%). Piperidine-1-carboxamidine 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. The residue was purified by flash chromatography on silica gel by consecutive elution with THF-MeOH (70 : 30 : 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. – 1H NMR (500 MHz, [D6]DMSO): δ = 7.46 [d, J = 8.8 Hz, 4H, C(2II)H, C(6II)H, C(2III)H, C(6III)H], 6.91 [d, J = 8.8 Hz, 4H, C(3III)H, C(4III)H, C(5III)H, C(7III)H], 7.56 [s, 1H, C(5IV)], 6.56 [s, 1H, C(8II)], 5.62 [s, 1H, C(3III)], 4.21–3.97 [m, 4H, C(10H2), C(6H), C(1I)H], 3.95–3.84 [m, 2H, C(1)H, C(5)H], 3.74 [m, 6H, 2 ArOCH3], 3.66 [bt, J = 5.0 Hz, 4H, piperidine, N-CH2], 3.26 [s, 3H, C(1I)OCH3]. 2.94 [s, 6H, N(CH2)3], 2.85 and 2.84 [dd, J = 14.0, 3.0 Hz, 1H, C(2I)H], [C(2II)H] 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[4IV]), C(6IV), and C(2IV)], 159.38 and 159.29 [C(4I)H, and (C4II)H], 150.92 and 150.87 [C(1I)I], and C(1I)II], 127.35 and 127.07 [C(2I)II], C(6I)II], C(6I)II], 113.32 and 113.26 [C(3II), C(5II)], C(3III), C(5III)], 99.34 and 98.94 [C(3) and C(8)], 91.83 [C(5IV)], 78.86 [C(5)], 67.60 [C(1I)], 69.19 [C(10)], 68.68 [C(6)], 58.16 [C(1I)OCH3], 55.07 and 55.05 (2 ArOCH3), 44.15 (piperidine, N-CH2), 39.12 [C2], overlapped by the solvent signal, detectable by DEPT-135], 36.39 [C(10H2)], 25.30 (piperidine, γ-CH2), 24.55 (piperidine, β-CH2), δ C(CH2) = δ C(H2)NaO(260.73) = calcld. C 65.79, H 7.14; found C 64.40, H 6.67. – HRMS ([+];ESI): m/z = 621.3288 (calcld. 621.3288 for C34H32N2O7, [M+H]+). 5,5-Bis(dimethylamino)-2-cyano-3-(R)-methoxy-[(1S,3S,5R,6R,8R)-3,8-bis-(4-methoxyphenyl)-2,4,7,9-tetraoxabicyclo[4.4.0]decan-5-yl][methyl]pent-2-4-dienenitrile (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 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-MeOH (9 : 1, CHC12-THF-MeOH (70 : 30 : 1.5), and CHC12-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. – 1H NMR (500 MHz, [D6]DMSO, 297 K):
\( \delta = 7.41 \) and 7.33 [2d, J = 8.8 Hz, 4H, C(II)H, C(III)H], 6.93 and 6.90 [2d, J = 8.8 Hz, 4H, C(II)H, C(III)H, C(IV)H, C(V)H], 5.65 [s, 1H, C(1)H], 5.57 [s, 1H, C(II)H], 4.54 [s, 1H, C(IV)H], 4.29 [d, J = 9.0 Hz, 1H, C(III)], 4.20–4.06 [m, 4H, C(5)H, C(6)H, C(10)H], 3.92 [s, 1H, C(1)H], 3.75 and 3.74 [2s, 6H, 2 ArOCH₃], 3.27 [s, 3H, C(1)OCH₃], 2.90 [s, 12H, 2 N(CH₃)₂]. – 13C NMR (125.76 MHz, \( \text{D}_8 \text{JDMSO} \)): \( \delta = 167.47 \) and 167.60 [C(IV)H] and C(III)H], 159.42 and 159.32 [C(4) and C(III)], 130.94 and 130.39 [C(1)H and C(III)], 127.44 and 127.24 [C(II)H], C(III)H, C(IV)H], 120.32 (CN), 113.30 and 113.20 [C(3)H, C(5)H, C(3)H], C(III)H], 99.45 [C(3)], 99.02 [C(8)], 89.59 [C(IV)H], 79.67 [C(1)H], 78.93 [C(5)], 69.75 [C(1)], 69.17 [C(10)], 68.27 [C(6)], 56.63 [C(1)OCH₃], 45.90 [C(IV)H], 40.71 [N(CH₃)₂]. – C₃H₂N₂O₇ (590.66) calculated N 6.48, H 6.48, N 9.49; found C 64.48, H 6.46, N 9.24. – HRMS (ESI): m/z = 591.2804 (calcd. 591.2807 for C₃H₂N₂O₇, [M+H]+). 613.2634 (calcd. 613.2638 for C₃H₂N₂O₇N₂, [M+Na]+), 629.2374 (calcd. 629.2377 for C₃H₂N₂O₇K, [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-ylmethyl)-pent-2,4-dienoitrile (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 rt 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 (63%), pale-yellow crystals; m.p. 222–224 °C. – IR (KBr): v = 2967, 2908, 2837 (OCH₃), 2208 (CN), 1599 (C=O), 1514, 1244, 1114, 1030, 827, 702, 776 cm⁻¹. – 1H NMR (500 MHz, \( \text{D}_8 \text{JDMSO} \)): \( \delta = 11.27 \) (bs, 1H, NH), 7.41 and 7.29 [2d, J = 8.7 Hz, 4H, C(II)H, C(III)H, C(IV)H, C(V)H], 6.94 and 6.87 [2d, J = 8.7 Hz, 4H, C(II)H, C(III)H, C(IV)H, C(V)H], 5.69 [s, 1H, C(5)H], 5.54 [s, 1H, C(3)H], 4.58 [d, J = 9 Hz, C(5)H], 4.25–4.08 [m, 4H, C(11)H, C(6)H, C(10)H], 3.94 [s, 1H, C(1)], 3.76 and 3.73 [2s, 6H, 2 ArOCH₃], 3.24 [3s, 3H, C(1)OCH₃], 3.05 [s, 6H, N(CH₃)₂]. – 13C NMR (125.76 MHz, \( \text{D}_8 \text{JDMSO} \)): \( \delta = 159.41 \) and 159.34 [C(II)H and C(IV)H], 130.89 and 130.40 [C(1)H and C(III)H], 127.42 and 127.17 [C(II)H, C(III)H, C(IV)H, C(V)H], 117.10 (CN), 113.35 and 113.21 [C(II)H, C(III)H, C(IV)H], 99.12 and 99.07 [C(3) and C(8)], 78.72 [C(5)], 77.58 [C(1)], 69.66 [C(1)], 69.21 [C(10)], 69.32 [C(6)], 57.17 [C(1)OCH₃], 55.09 [ArOCH₃]. – C₂₉H₂₃N₇O₇ (563.59) calculated 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...
and extracted three times with CH

After 48 h at r. t., the mixture was diluted with water (5 mL) and then a mixture of ethanol (5 mL) and 37% aqueous HCl (0.6 mL). 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 39. Yield 70 mg (48%), pale-yellow crystals; m. p. >280 °C (dec.). – Rₐ = 0.58 (CHCl₃-MeOH, 1:1). – FT-IR (ATR): ν = 3118 (OH assoc.), 2984, 2803, 2205 (CN), 1609 (C=O), 1381, 1096 cm⁻¹. – 1H NMR (500 MHz, D₂O/DMSO): δ = 5.97 [s, 1H, C(5)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)H₂], 3.68–3.57 [m, 1H, C(1)H₆], 3.35 [s, 3H, OCH₃], 3.20 [s, 6H, N(CH₃)₂]. – 13C NMR (125.76 MHz, D₂O/DMSO): δ = 167.70 (C=O), 161.32 [C(4)’, 156.41 [C(6)’], 121.63 [CN], 95.54 [C(5)’], 84.64 [C(5)], 83.79 [C(3)’], 75.76, 75.17, 72.52 [C(2)], C(3), and C(4)], 65.22 [C(1)H₆], 59.88 [OCH₃].

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.). – Rₐ = 0.39 (CHCl₃-MeOH, 7:3). – FT-IR (ATR): ν = 3333 (OH assoc.), 2933, 2201 (CN), 1592 (C=O), 1382, 1066, 996 cm⁻¹. – 1H NMR (500 MHz, D₂O/DMSO): δ = 5.84 [s, 1H, C(5)H], 3.88–3.80 [m, 1H, C(3)H], 3.80–3.68 [m, 4H, C(1)H₂(C), C(2)H], C(4)H, C(5)H], 3.64 and 3.63 [2d, J = 12.0, 6.8 Hz, C(1)H₆], 3.34 [s, 3H, C(5)OCH₃], 3.17 [bs, 6H, N(CH₃)₃]. – 13C NMR (125.76 MHz, D₂O/DMSO): δ = 167.25 (C=O), 161.64 [C(4)’], 155.83 [C(6)’], 121.85 (CN), 97.20 [C(5)’], 85.56 [C(3)’], 83.53 [C(5)], 75.54 [C(3)], 74.67 and 72.63 [C(2) and C(4)], 65.36 [C(1)], 61.67 [N(CH₃)₂]. – HRMS (+)-ESI: m/z = 364.1474 (calcd. 364.1484 for C₁₈H₂₃N₄O₆Na, [M+Na]⁺).