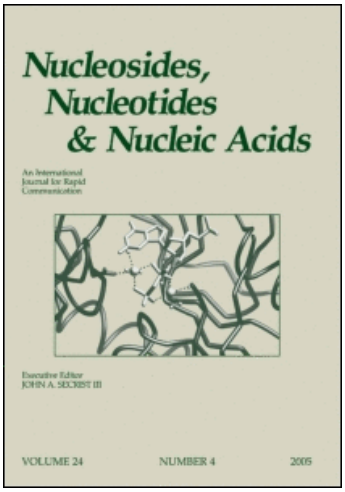

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New Acyclic Quinoxaline Nucleosides. Synthesis and Anti-Hiv Activity

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NEW ACYCLIC QUINOXALINE NUCLEOSIDES. SYNTHESIS AND ANTI-HIV ACTIVITY

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□ *A series of acyclonucleosides substituted 1-(4,5-dihydroxypentyl) (**13-8**) and 2-(4,5-dihydroxypentyloxy)quinoxalines (**19-24**) were synthesized by the sharpless asymmetric dihydroxylation of the derivatives **1-6** and **7-12**, respectively. Treatment of the quinoxaline base **26** with (*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl-p-toluenesulfonate (**27**) in the presence of NaH/DMF furnished **28**. Acid hydrolysis of **28** gave 1-(2,3-dihydroxypropyl)-6,7-dimethyl-quinoxaline-2-one (**29**). Alternatively, **29** was prepared by sharpless dihydroxylation of **30**. All the compounds were evaluated for their in vitro anti-HIV-1 and HIV-2 in MT-4 cell and found inactive, except **29**, which showed inhibition of HIV-1 with* EC_{50} *value of 0.15 ± 0.1 μg/ml and a therapeutic index (*SI*) of 73.*

Keywords Acyclonucleosides; alkylation; antiviral activity; glycosides; quinoxalines

INTRODUCTION

Several acyclonucleoside analogues are known to posses antiviral chemotherapeutic activity.[1–4] Acyclovir (ACV, Zovirax) **1**,[5,6] the potent antiherpetic drug,[7,8] and 9-(2-phosphonylmethoxyethyl)adenine (PMEA), (*S*)-1-(3-hydroxy-2-phosphonylmethoxypropyl) adenine (HPMPA),[9] (*RS*)-9-[4-hydroxy-2-(hydroxymethyl)butyl]guanine (HBG) and (9-[(1,3-dihydroxy-2-propoxy)methyl] guanine (DHPG) **2**,[10,11] are examples of

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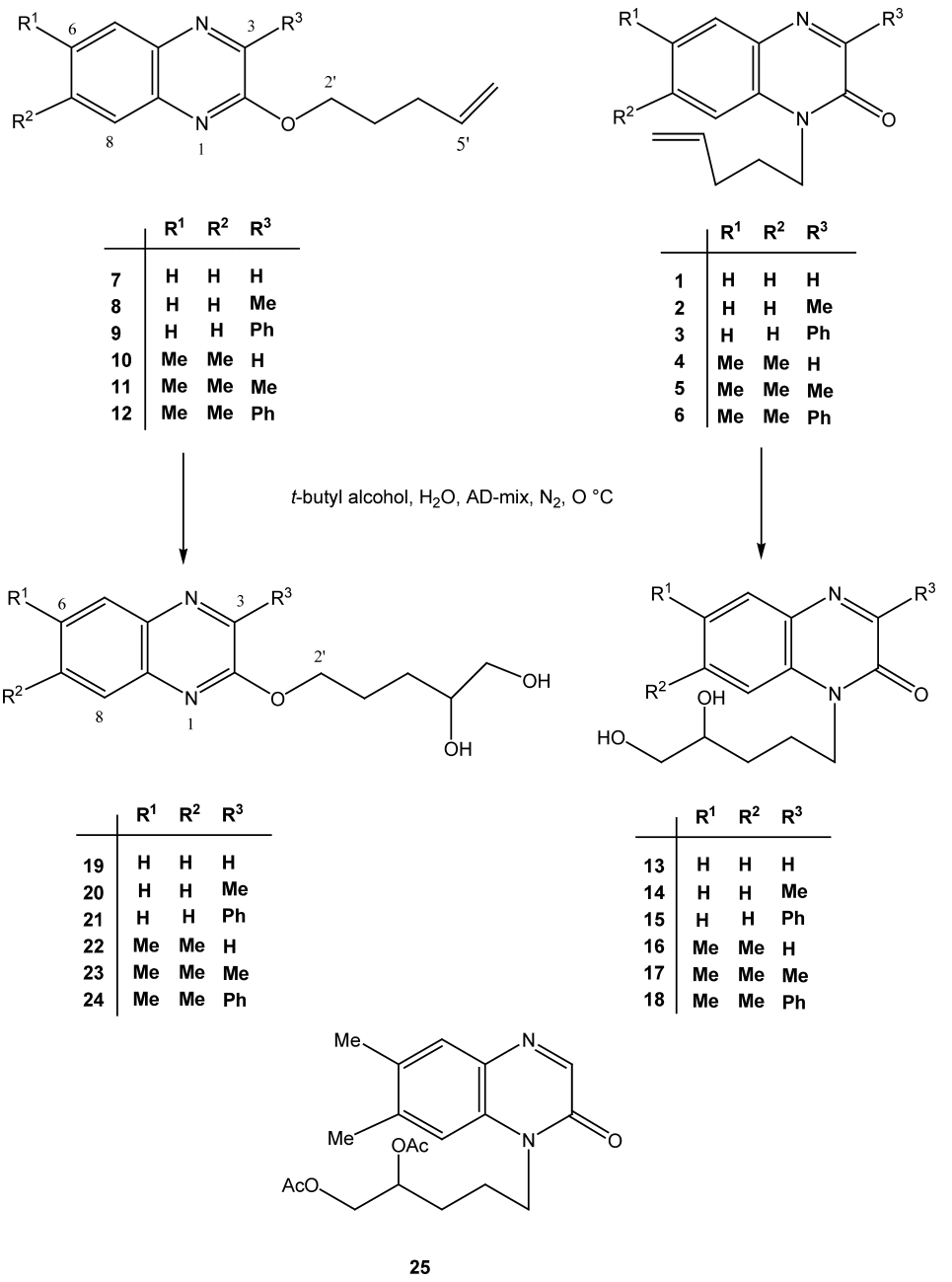
such potent antiviral agents. The structure-activity relationship studies have shown that the side chains of acyclonucleosides play a crucial role in the interaction of the acyclonucleosides with their antiviral target enzymes[12] (phosphorylation). Furthermore, recent reviews in the field of acyclonucleosides have been reported.[13] The pharmacological applications of quinoxalines are reported as angiotension II receptor antagonists,[14] *N*-methyl-D-aspartate (NMDA) anagonists,[15] anti-inflammatory,[16] antidepressant-tranquilizing,[17] antitumor agents,[18,19] and anti-hepatitis B virus (HBV) activity.[20] The biological importance of these derivatives prompted us to synthesize, recently, some homo unsaturated acyclocnucleoside quinoxaline derivatives,[21] meanwhile our present work is a continuation for our recent efforts by preparation of their dihydroxylated derivatives and evaluation of their anti-HIV activity as well as an extension work for El-Ashry et al.[20]

RESULTS AND DISCUSSION

In previous work, the preparation of *O*- and *N*-alkyl[20] and allyl[21] substituted quinoxalines have been described. By following the similar method, the 1-(pent-4-enyl)quinoxaline **1-6** and the 2-(pentyl-4-enyloxy)quinoxalines **7-12** derivatives,[22] have been prepared from the regioselective alkylation of quinoxalines with 5-bromo-1-pentene and allyl bromide, respectively, in the presence of NaH. As ongoing program for the synthesis of acyclonucleosides,[23–25] we report here the synthesis of new analogues of 4,5-dihydroxy-pentyl-quinoxalinone acyclonucleosides with evaluation of their anti-HIV activity.

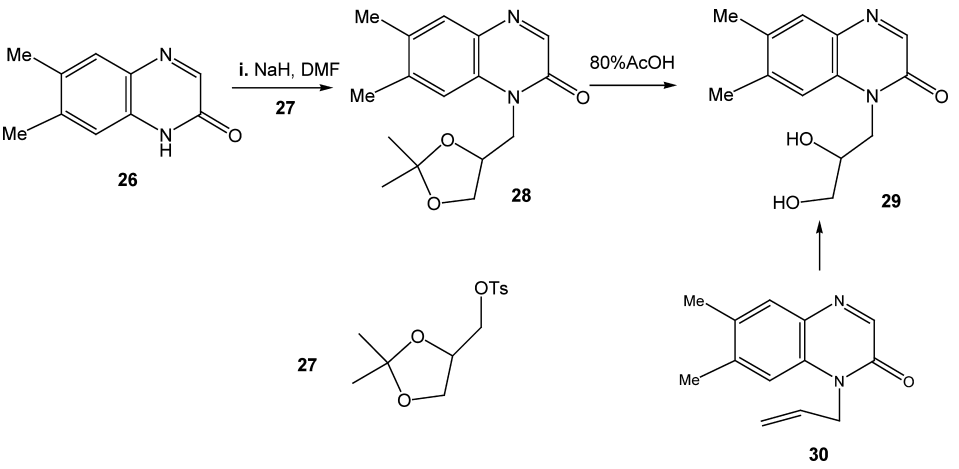
Sharpless asymmetric dihydroxylation[26] of **1-6** and **7-12** with AD-mix under N_2 at 0°C for 24 hours afforded, after chromatographic purification, the acyclic *N*-homonucleosides **13-18** (57–81%) and the *O*-analogues **19-24** (58–82%), respectively, as outlined in Scheme 1

The structures of **13-24** were assigned from their ^{1}H, ^{13}C NMR, and mass spectra. The ^{1}HNMR spectra (in $CDCl_3$) of **13-18** showed similar pattern of H-5 (δ 7.73–7.04) and H-8 (δ 7.95–7.51) aromatic protons, while H-5 and H-8 of **16** (in DMOS-d_6) appeared at δ 6.96 and 7.21, respectively. The singlet at higher field (δ 8.20, 7.52, and 8.41, in $CDCl_3$) were attributed to H-3 of compounds **13**, **19,** and **22**, respectively, meanwhile the same proton of **13** (in DMSO-d_6) appeared at δ 7.52. CH_2_1′ of **13-18** appeared as multiplets (δ 4.54–4.22), meanwhile CH_2_2′ of the *O*-analogues **19-24** appeared as multiplets or triplets at the region δ 4.53–4.45 ($J = 6.5$ Hz). The multiplets at **13-18** (except **16**) at the region δ 3.82–3.73 were assigned to H-4, while the doublets of doublets oriented at the region δ 3.64–3.56 and δ 3.45–3.38 were attributed to the geminal H-5′a and H-5′b, respectively, ($J_{4',5a'} \sim$ 3.5 Hz, $J_{4',5b'} \sim 7.5$ Hz $J_{5'a,5'b} = 11.0$ Hz). Similarly, CH_2_2′—CH_2_6′a,b were fully analyzed. The ^{13}C NMR spectra of **13-24** were well established



SCHEME 1 Preparation of compounds **13-24** by sharpless oxidation of **1-12**.

(see Experimental section), and contained similar resonance signals of the aromatic carbons ring C-3–C-8. In the ^{13}C NMR spectra of **19-24**, the C-2 resonated relatively at higher field (δ_C 178.9–175.0) in comparison to the same carbon atom of the *O*-analogues **13-18** (δ_C 158.2–154.4) due to the



SCHEME 2 Synthesis of title compounds **28**, **29**.

difference in the deshielding nature between N and O atoms. On this basis, C-1′ of **13-18** resonated relatively at lower field (δ_C 42.4–41.9) in comparison to the C-2′ of the *O*-analogues **19-24** (δ_C 66.6–65.9).

Compound **13** was selected for the ^{1}H and ^{13}C NMR analysis. In the ^{1}H NMR (HMQC)[27] spectrum of **13**, the two multiplets at δ_H 1.85 and 1.53 (δ_C 23.7 and 30.0) were assigned to H-2′ and H-3′ (C-2′ and C-3′, respectively) by spin decoupling experiment. The site of alkylation of **13** at N-1 was visible in the ROESY spectra, where the CH_2-1′ protons at δ_H 4.27 showed cross signals to the aromatic H-8 at δ_H 7.80, but not to H-5 of the quinoxaline ring at δ_H 7.52.

The proton spin system of **13** was further identified from DFQ-COSY[28] spectra, where the multiplets of H-4′ at the region δ_H 3.76 were found to correlate with the singlet at δ_C 71.7. From the gradient selected HMBC[29] spectra of **13**, CH_2-1′ proton at δ_H 4.27 showed $^3J_{C,H}$ couplings with C=O at δ_C 155.0, and $^2J_{C,H}$ coupling with C-2′ at δ_C 23.7. The quinoxaline carbon atoms were fully analyzed and are in agreement with those of the known derivatives prepared previously.[21]

The structure of **16** was further elucidated by preparation of the diacetate derivative **25** (87%).

Next, the quinoxaline base **26** was treated with (*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl-*p*-toluenesulfonate (**27**), following the reported method,[30] in the presence of NaH and DMF at 23°C to give, after chromatography, **28** (65%). Acid hydrolysis of **28** by 80% HOAc at 23°C afforded the hydroxylated acyclonucleoside **29** (78%). Alternatively, **29** was prepared, in 85% yield, following sharpless dihydroxylation method, from **30** in the presence of AD-mix (Scheme 2).

The structural assignment of **28** and **29** were followed from the ^{1}H NMR and mass spectra. The aromatic protons H-3, H-8 and H-5 were appeared

as singlets at δ_H 8.33, 7.56, and 7.53, respectively, while the multiplet at δ_H 3.91–3.76 was attributed to H-3′a and H-3′b. CH_2_1′ appeared at a multiplet at δ_H 3.38 and the two singlets at δ_H 2.41 and 2.37 were assigned to the aromatic methyl groups at C-6 and C-7.

IN VITRO anti-HIV-ASSAY

Compounds **13-24** and **29** were evaluated for their in vitro anti-HIV activity using the MT-4/MTT assay.[31] All the tested compounds are inactive, except **29** which found to be the only compound from the series inhibiting HIV-1 replication in cell culture in comparison to the standard antiviral drugs efavirenz[32] and capravirine.[33] Compound **29** showed an EC_{50} of 0.15 ± 0.1 μg/mL and a CC_{50} of 10.95 ± 0.1 μg/mL, resulting in a selectivity index of 73.

Based on the chemical structure and the fact that compound **29**, inhibits HIV-1 in comparison to **13-25**, it can be concluded that the hydroxylated alkyl residue play a major role in the antiviral activity in such molecules.

EXPERIMENTAL

Melting points were determined on a Büchi 510 melting point apparatus and the values are uncorrected. NMR spectra were measured with Bruker AC 250 (250 MHz) using TMS as internal starndard. Mass spectra were measured with FAB-MS modified Finningan MAT 312/AMD 5000 spectrometer at 790 eV and T = 70 MALDI-MS using Na^+ as dropping ion.

General procedure of oxidation reaction. To a cold (~0°C) mixture of *t*-butyl alcohol (45 mL), water (45 mL), and AD-mix-α (14.0 g) was added the compounds **1-12** (10.0 mmol) under nitrogen. The reaction mixture was stirred at 0°C for 5 hours and then stored in the refrigerator for at least 24 hours. At the end of the reaction time, add solid Na_2SO_3 (14.5 g) was added and stirred for 30 minutes to decompose the oxidant. The mixture was extracted with ethyl acetate (4 × 30 mL), dried ($MgSO_4$), filtered, and evaporated to dryness and the residue was poured on silica gel column (40 g). Elution, in gradient, with MeOH (0–10%) afforded the *N*-analogues, 6,7-disubstituted 1-(4,5-dihydroxypentyl) quinoxalin-2-one derivatives (**13-18**) and the 2-(4,5-dihydroxypentyloxy)quinoxaline derivatives (**19-24**).

1-(4,5-Dihydroxypentyl)quinoxalin-2-one (**13**). From **1** (2.14 g). Yield: 1.86 g (75%), brown oil. ^{1}H NMR ($CDCl_3$): δ 8.20 (s, 1H, H-3); 7.80 (dd, 1H, J = 1.5 Hz, 8.2 Hz, H-8); 7.52 (t, 1H, J = 7.6 Hz, H-5); 7.36–7.24 (m, 2H, H-6, H-7); 4.27 (m, 2H, CH_2_1′); 3.76 (m, 1H, H-4′); 3.58 (dd, 1H, $J_{4',5'a}$ = 3.4 Hz, H-5′a); 3.45 (dd, 1H, $J_{4',5b'}$ = 7.2 Hz, $J_{5'a,5'b}$ = 11.0 Hz, H-5′b); 1.85 (m, 2H, CH_2_2′); 1.53 (m, 2H, CH_2_3′). ^{13}C NMR ($CDCl_3$): δ 155.0 (C=O); 150.0 (C-3); 133.8 (C-4a); 132.3 (C-8a); 131.2 (C-7); 130.8 (C-6); 123.9 (C-5); 114.0

(C-8); 71.7 (C-4′); 66.7 (C-5′); 42.0 (C-1′); 30.0 (C-3′); 23.7 (C-2′). Anal. calc. for $C_{13}H_{16}N_2O_3$ (248.28): C, 62.89; H, 6.50; N, 11.28. Found: C, MS (FAB) *m/z* 271 $[M+Na]^+$.

1-(4,5-Dihydroxypentyl)-3-methylquinoxalin-2-one (**14**). From **2** (2.62 g). Yield: 2.12 g (81%), m.p. 66–68°C, reddish powder. ^{1}H NMR ($CDCl_3$): δ 7.78 (d, 1H, $J = 8.0$ Hz, H-8); 7.48 (t, 1H, $J = 7.6$ Hz, H-5); 7.45–7.25 (m, 2H, H-6, H-7); 4.26 (m, 2H, CH_2-1′); 3.79 (m, 1H, H-4′); 3.62 (dd, 1H, $J_{4',5'a} = 3.5$ Hz, H-5′a); 3.30 (br s., 2H, 2xOH); 3.45 (dd, 1H, $J_{4',5b'} = 7.2$ Hz, $J_{5'a,5'b} = 11.0$ Hz, H-5′b); 1.88 (m, 2H, CH_2-2′); 1.56 (m, 2H, CH_2-3′). ^{13}C NMR ($CDCl_3$): δ 158.2 (C=O); 155.1 (C-3); 133.1 (C-4a); 132.3 (C-8a); 129.8 (C-6, C-7); 123.7 (C-5); 113.7 (C-8); 71.7 (C-4′); 66.7 (C-5′); 42.2 (C-1′); 29.9 (C-3′); 23.7 (C-2′); 21.5 (Me). Anal. calc. for $C_{14}H_{18}N_2O_3$ (262.30): C, 64.10, H, 6.92, N, 10.68. Found: C, 63.84, H, 6.81, N, 10.47. MS: m/z 263 $(M+H)^+$.

1-(4,5-Dihydroxypentyl)-3-phenylquinoxalin-2-one (**15**). From **3** (2.90 g). Yield: 1.84 g (57%), m.p. 76–79°C, white powder. ^{1}H NMR ($CDCl_3$): δ 8.26 (m, 2H, Ar-H); 7.93 (m, 2H, Ar-H); 7.55–7.24 (m, 5H, Ar-H); 4.30 (m, 2H, CH_2-1′); 3.77 (m, 1H, H-4′); 3.62 (dd, 1H, $J_{4',5'a} = 3.1$ Hz, H-5′a); 3.45 (dd, 1H, $J_{4',5b'} = 7.3$ Hz, $J_{5'a,5'b} = 11.0$ Hz, H-5′b); 2.84 (br s., 2H, 2xOH); 1.88 (m, 2H, CH_2-2′); 1.57 (m, 2H, CH_2-3′). ^{13}C NMR ($CDCl_3$): δ 154.5 (C=O); 153.9 (C-3); 135.9 (C-4a); 133.4 (Ar-C); 132.3 (C-8a); 130.7 (C-7); 130.4 (C-6); 130.3, 129.5, 128.0 (Ar-C); 123.7 (C-5); 113.6 (C-8); 71.6 (C-4′); 66.7 (C-5′); 42.4 (C-1′); 29.9 (C-3′); 23.5 (C-2′). Anal. calc. for $C_{19}H_{20}N_2O_3$ (324.37): C, 70.35, H, 6.21, N, 8.64. Found: C, 70.12, H, 6.11, N, 8.43. MS: m/z 325 $(M+H)^+$.

6,7-Dimethyl-1-(4,5-dihydroxypentl)quinoxalin-2-one (**16**). From **4** (2.42 g). Yield: 2.18 g (79%), m.p. 230–232°C, white powder. ^{1}H NMR (DMSO-d_6): δ 7.52 (s, 1H, H-3); 7.21 (s, 1H, H-8); 6.96 (s, 1H, H-5); 4.51 (br s., 1H, C_4-OH); 4.09 (t, 1H, $J = 5.1$ Hz, C_5-OH); 3.48 (m, 2H, CH_2-1′); 3.29 (m, 3H, CH_2-5′, H-4′); 1.65 (m, 2H, CH_2-2′); 1.35 (m, 2H, CH_2-3′). Anal. calc. for $C_{15}H_{20}N_2O_3$ (276.33): C, 65.20, H, 7.30, N, 10.14. Found: C, 64.92, H, 7.15, N, 9.87. MS: m/z 277 $(M+H)^+$.

3,6,7-Trimethyl-1-(4,5-dihydroxypentyl)quinoxalin-2-one (**17**). From **5** (2.56 g). Yield: 2.06 g (71%), m.p. 129–131°C, reddish powder. ^{1}H NMR ($CDCl_3$): δ 7.51 (s, 1H, H-8); 7.49 (s, 1H, H-5); 4.45 (m, 2H, CH_2-1′); 3.82 (m, 1H, H-4′); 3.64 (dd, 1H, $J_{4',5'a} = 3.1$ Hz, H-5′a); 3.47 (dd, 1H, $J_{4',5b'} = 7.3$ Hz, $J_{5'a,5'b} = 11.0$ Hz, H-5′b); 2.50, 2.36, 2.29 (3xs., 9H, 3xMe); 1.87 (m, 2H, CH_2-2′); 1.56 (m, 2H, CH_2-3′). ^{13}C NMR ($CDCl_3$): δ 156.5 (C = O); 155.0 (C-3); 139.2 (C-4a); 132.4 (C-7); 131.3 (C-6); 129.9 (C-8a); 129.6 (C-5); 114.0 (C-8); 71.5 (C-4′); 66.6 (C-5′); 41.9 (C-1′); 29.7 (C-3′); 23.5 (C-2′); 21.2, 20.4, 19.0 (3xMe). Anal. calc. for $C_{16}H_{22}N_2O_3$ (290.36): C, 66.18, H, 7.64, N, 9.65. Found: C, 65.95, H, 7.49, N, 9.41. MS: m/z 291 $(M+H)^+$.

6,7-Dimethyl-1-(4,5-dihydroxypentyl)-3-phenylquinoxalin-2-one (**18**). From **6** (3.18 g). Yield: 2.07 g (59%), yellow crystals, 121–124°C. ^{1}H NMR ($CDCl_3$): δ 8.19 (m, 2H, Ar-H); 7.62 (s, 1H, H-8); 7.38 (m, 3H, Ar-H);

7.04 (s, 1H, H-5); 4.22 (m, 2H, CH_2_1′); 3.73 (m, 1H, H-4′); 3.56 (dd, 1H, $J_{4',5'a}$ = 3.0 Hz, H-5′a); 3.38 (dd, 1H, $J_{4',5b'}$ = 6.5 Hz, $J_{5'a,5'b}$ = 11.1 Hz, H-5′b); 2.34, 2.28 (2xs, 6H, 2xMe); 1.86 (m, 2H, CH_2_2′); 1.51 (m, 2H, CH_2_3′). ^{13}C NMR ($CDCl_3$): δ 154.4 (C=O); 152.4 (C-3); 140.3 (C-4a); 136.1 (C-7); 132.7 (C-6); 131.8, 130.5, 130.1 (Ar-C); 129.8 (C-8a); 129.3 (C-5); 127.8 (Ar-C); 113.9 (C-8); 71.5 (C-4′); 66.5 (C-5′); 42.1 (C-1′); 29.8 (C-3′); 23.4 (C-2′); 20.5, 19.0 (2xMe). Anal. calc. for $C_{21}H_{24}N_2O_3$ (352.43): C, 71.57, H, 6.86, N, 7.95. Found: C, 71.33, H, 6.76, N, 7.76. MS: m/z 353 $(M+H)^+$.

5-(Quinoxalin-2-yloxy)pentane-1,2-diol (**19**). From **7** (2.48 g). Yield: 1.59 g (64%), white powder, m.p. 81–83°C. ^{1}H NMR ($CDCl_3$): δ 8.41 (s, 1H, H-3); 7.95 (dd, 1H, J = 1.5 Hz, 8.1 Hz, H-8); 7.73 (t, 1H, J = 7.4 Hz, H-5); 7.64–7.47 (m, 2H, H-6, H-7); 4.47 (m, 2H, CH_2_2′); 3.52 (m, 1H, H-5′); 3.68 (dd, 1H, $J_{5',6'a}$ = 3.5 Hz, H-6′a); 3.49 (dd, 1H, $J_{5',6b'}$ = 7.4 Hz, $J_{6'a,6'b}$ = 11.0 Hz, H-6′b); 1.96 (m, 2H, CH_2_4′); 1.63 (m, 2H, CH_2_5′). ^{13}C NMR ($CDCl_3$): δ 175.9 (C-2); 140.4 (C-8a); 139.8 (C-4a); 138.2 (C-3); 130.2 (C-7); 128.9 (C-5); 127.1 (C-8); 126.6 (C-6); 71.9 (C-5′); 66.7 (C-6′); 66.3 (C-2′); 29.6 (C-4′); 25.0 (C-3′). Anal. calc. for $C_{13}H_{16}N_2O_3$ (248.28): C, 62.89, H, 6.50, N, 11.28. Found: C, 62.73, H, 6.37, N, 11.03. MS: m/z 249 $(M+H)^+$.

5-(2-Methylquinoxalin-3-yloxy)pentane-1,2-diol (**20**). From **8** (2.62 g). Yield: 1.99 g (76%), white powder, m.p. 63–65°C. ^{1}H NMR ($CDCl_3$): δ 7.91–7.48 (m, 4H, H-5–H-8); 4.51 (t, 2H, J = 6.5 Hz, CH_2_2′); 3.84 (m, 1H, H-5′); 3.70 (dd, 1H, $J_{5',6'a}$ = 3.1 Hz, H-6′a); 3.49 (dd, 1H, $J_{5',6b'}$ = 7.5 Hz, $J_{6'a,6'b}$ = 11.0 Hz, H-6′b); 2.01 (m, 2H, CH_2_4′); 1.64 (m, 2H, CH_2_5′). ^{13}C NMR ($CDCl_3$): δ 178.1 (C-2); 148.2 (C-3); 139.9 (C-8a); 138.6 (C-4a); 128.9 (C-7); 128.1 (C-5); 126.7 (C-8); 126.4 (C-6); 71.9 (C-5′); 66.8 (C-6′); 66.3 (C-2′); 29.7 (C-4′); 25.1 (C-3′); 20.4 (Me). Anal. calc. for $C_{14}H_{18}N_2O_3$ (262.30): C, 64.10, H, 6.92, N, 10.68. Found: C, 63.89, H, 6.79, N, 10.45. MS: m/z 263 $(M+H)^+$.

5-(2-Phenylquinoxalin-3-yloxy)pentane-1,2-diol (**21**). From **9** (3.24 g). Yield: 2.23 g (69%), white powder, m.p. 58–61°C. ^{1}H NMR ($CDCl_3$): δ 7.62 (m, 2H, H-8); 7.49 (m, 2H, H-5); 4.45 (m, 2H, CH_2_2′); 3.82 (m, 1H, H-5′); 3.67 (dd, 1H, $J_{5',6'a}$ = 3.0 Hz, H-6′a); 3.47 (dd, 1H, $J_{5',6b'}$ = 7.6 Hz, $J_{6'a,6'b}$ = 11.1 Hz, H-5′b); 2.54, 2.37 (2xs, 9H, 3xMe); 1.95 (m, 2H, CH_2_3′); 1.63 (m, 2H, CH_2_4′). ^{13}C NMR ($CDCl_3$): δ 177.0 (C-2); 146.7 (C-3); 139.9 (C-8a); 138.9 (C-4a); 136.2 (Ar-C); 129.7 (Ar-C, C-7); 129.0 (C-5); 128.2 (Ar-C, C-8); 126.8, 126.6 (Ar-C); 71.8 (C-5′); 66.8 (C-6′); 66.6 (C-2′); 29.7 (C-4′); 24.9 (C-3′). Anal. calc. for $C_{19}H_{20}N_2O_3$ (324.37): C, 70.35, H, 6.21, N, 8.64. Found: C, 70.12, H, 6.03, N, 8.43. MS: m/z 325 $(M+H)^+$

5-(6,7-Dimethylquinoxalin-2-yloxy)pentane-1,2-diol (**22**). From **10** (2.76 g). Yield: 1.60 g (58%), white crystals, m.p. 113;115°C. ^{1}H NMR ($CDCl_3$): δ 8.32 (m, 1H, H-3); 7.71 (m, 2H, H-8); 7.54 (s, 1H, H-5); 4.45 (t, 2H, J = 6.5 Hz, CH_2_2′); 3.82 (m, 1H, H-5′); 3.69 (dd, 1H, $J_{5',6'a}$ = 3.1 Hz, H-6′a); 3.50 (dd, 1H, $J_{5',6b'}$ = 7.5 Hz, $J_{6'a,6'b}$ = 11.1 Hz, H-6′b); 3.19 (br s., 2H,

2xOH); 2.40 (2xs, 6H, 2xMe); 1.93 (m, 2H, CH_2_3′); 1.64 (m, 2H, CH_2_4′). ^{13}C NMR ($CDCl_3$): δ 175.0 (C-2); 140.3 (C-7); 138.7 (C-6); 138.2 (C-8a); 137.4 (C-3); 136.2 (C-4a); 128.0 (C-5); 126.4 (C-8); 71.8 (C-5′); 66.6 (C-6′); 65.9 (C-2′); 29.4 (C-4′); 24.9 (C-3′); 20.1, 19.7 (2xMe). Anal. calc. for $C_{15}H_{20}N_2O_3$ (276.33): C, 65.20, H, 7.30, N, 10.14. Found: C, 64.89, H, 7.17, N, 9.88. MS: m/z 277 $(M+H)^+$.

5-(2,6,7-Trimethylquinoxalin-3-yloxy)pentane-1,2-diol (**23**). From **11** (2.90 g). Yield: 2.38 g (82%), white powder, m.p. 104–107°C. ^{1}H NMR ($CDCl_3$): δ 7.62 (s, 1H, H-8); 7.49 (s, 1H, H-5); 4.45 (m, 2H, CH_2_2′); 3.82 (m, 1H, H-6′); 3.64 (dd, 1H, $J_{5',6'a}$ = 3.0 Hz, H-5′a); 3.47 (dd, 1H, $J_{5',6b'}$ = 7.6 Hz, $J_{6'a,6'b}$ = 11.0 Hz, H-6′b); 2.54, 2.37 (2xs., 6H, 2xMe); 1.95 (m, 2H, CH_2_3′); 1.63 (m, 2H, CH_2_4′). ^{13}C NMR ($CDCl_3$): δ 178.9 (C-2); 146.8 (C-7); 138.9 (C-3); 138.3 (C-6); 137.1 (C-8a); 129.4 (C-5); 126.5 (C-8); 71.8 (C-5′); 66.7 (C-6′); 66.0 (C-2′); 29.6 (C-4′); 25.0 (C-3′); 20.2, 20.1, 19.9 (3xMe). Anal. calc. for $C_{16}H_{22}N_2O_3$ (290.36): C, 66.18, H, 7.64, N, 9.65. Found: C, 65.87, H, 7.53, N, 9.42. MS: m/z 291 $(M+H)^+$.

5-(6,7-Dimethyl-2-phenylquinoxalin-3-yloxy)pentane-1,2-diol (**24**). From **12** (3.52 g). Yield: 2.25 g (64%), white powder, m.p. 79–81°C. ^{1}H NMR ($CDCl_3$): δ 8.05 (m, 2H, Ar-H); 7.79 (s, 1H, H-8); 7.58 (s, 1H, H-5); 7.44 (m, 3H, Ar-H); 4.53 (m, 2H, CH_2_2′); 3.73 (m, 1H, H-4′); 3.63 (dd, 1H, $J_{5',6'a}$ = 3.1 Hz, H-6′a); 3.41 (dd, 1H, $J_{5',6b'}$ = 7.6 Hz, $J_{6'a,6'b}$ = 11.0 Hz, H-6′b); 2.43, 2.42 (2xs., 6H, 2xMe); 1.95 (m, 2H, CH_2_3′); 1.60 (m, 2H, CH_2_4′). ^{13}C NMR ($CDCl_3$): δ 175.3 (C-2); 145.3 (C-7); 138.9 (C-6); 138.7 (C-8a); 138.3 (C-3); 137.6 (C-4a); 136.4, 129.4, 129.2 (Ar-C); 128.1 (C-5); 127.3 (Ar-C); 125.9 (C-8); 71.6 (C-5′); 66.6 (C-6′); 66.1 (C-2′); 29.5 (C-4′); 24.7 (C-3′); 20.1, 20.1, 19.8 (3xMe). Anal. calc. for $C_{21}H_{24}N_2O_3$ (352.43): C, 71.57, H, 6.86, N, 7.95. Found: C, 71.34, H, 6.69, N, 7.72. MS: m/z 353 $(M+H)^+$.

1-(4,5-Diacetoxypentyl)-6,7-dimethylquinoxalin-2-one (**25**). To a solution of **16** (0.30 g, 1.08 mmol) in dry pyridine (7 mL) was added acetic anhydride (4 mL) and the mixture was kept at 23°C for 16 hours. The mixture was evaporated to dryness and co-evaporated with EtOH (4 × 15 mL) to give a crude product, which was purified on column of silica gel (10 g). Elution with Pet. ether-ethyl acetate (50:3) afforded **25** (0.34 g, 87%) as a white powder, m.p. 176–179°C. ^{1}H NMR ($CDCl_3$): δ 7.78 (s, 1H, H-3); 7.25 (s, 1H, H-8); 7.08 (s, 1H, H-5); 5.16 (m, 1H, H-4′); 4.26 (m, 2H, CH_2_5′); 4.05 (dd, 2H, J = 6.5 Hz, 11.0 Hz, CH_2_1′); 2.46, 2.41 (2xs, 6H, 2xMe); 2.19, 2.17 (2xs, 6H, 2xOAc); 1.88–1.67 (m, 3H, CH_2_2′, CH_2_3′). Anal. calc. for $C_{19}H_{24}N_2O_5$ (360.40): C, 63.32; H, 6.71; N, 7.77. Found: C, 63.02; H, 6.65; N, 7.39. MS: m/z 361 $(M+H)^+$.

6,7-Dimethyl-(*R*)-1-(2,2-dimethyl-dioxlan-4-ylmethyl)-quinoxaline-2-one (28). To a stirrred solution of **26** (1.50 g, 8.61 mmol) in DMF (15 ml) containing NaH (0.36 g, 15.0 mmol) was added (*R*)-2,2-dimethyl-1,3-dioxolan-4-ylmethyl-*p*-toluenesulfonate (**27**) (3.10 g, 10.33 mmol). The mixture was stirred at 23°C for 4 hours, then filtered. The filtrate was

evaporated to dryness to give an oil which was purified on column of silica gel using, in gradient, MeOH (0–2%) and CH_2Cl_2 as eluent furnishing **28** (1.69 g, 65%) as a pure oil. ^{1}H NMR ($CDCl_3$): δ 8.30 (m, 1H, H-3); 7.54 (s, 1H, H-8); 7.51 (s, 1H, H-5); 4.51 (m, 1H, H-2′); 4.07 (dd, 1H, $J_{2',3'a}$ = 3.7 Hz, H-3′a); 3.68 (dd, 1H, $J_{2',3b'}$ = 6.3 Hz, $J_{5'a,5'b}$ = 10.5 Hz, H-3′b); 3.48 (m, 2H, CH_2_1′); 2.36, 2.30 (2xs, 6H, 2xMe); 1.45, 1.40 (2xs, 6H, CMe_2). Anal. calc. for $C_{16}H_{20}N_2O_3$ (288.34): C, 66.65, H, 6.99, N, 9.72. Found: C, 66.42, H, 6.82, N, 9.51. MS: m/z ($C_{17}H_{22}N_2O_3$) 325 $[M+Na]^+$.

(*S*)-1-(2,3-Dihydroxypropyl)-6,7-Dimethyl-Quinoxaline-2-one (29)

Method A. A solution of **28** (1.10 g, 3.64 mmol) in 80% HOAc (20 mL) was stirred at 23°C for 16 hours. The mixture was evaporated to dryness and the residue was co-evaporated with EtOH (4 × 20 mL). The residue was poured on column of silica gel (20 g) and eluted, in gradient, with MeOH (0–10%) and CH_2Cl_2 as eluent to afford **29** (0.70 g, 78%), m.p. 145–148°C. ^{1}H NMR ($CDCl_3$): δ 8.33 (s, 1H, H-3); 7.56 (s, 1H, H-8); 7.53 (s, 1H, H-5); 3.91–3.76 (m, 2H, H-3′a, H-3′b); 3.38 (m, 2H, CH_2_1′); 2.41, 2.37 (2xs, 6H, 2xMe). Anal. calc. for $C_{13}H_{16}N_2O_3$ (248.28): C, 62.89, H, 6.50, N, 11.28. Found: C, 62.62, H, 6.39, N, 11.01. MS: m/z 249 $(M+H)^+$.

Method B. Compound **30** (0.50 g, 2.33 mmol) was oxidized with AD-mix-α (14.0 g) by following the preparation procedure of **13-18**, furnishing **29** (0.47 g, 85%). The product has identical physical properties in comparison for those prepared in Method A.

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