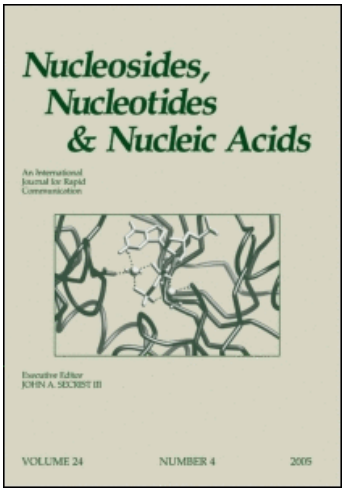

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Novel Enamine Derivatives of 5,6-Dihydro-2'-Deoxyuridine Formed in Reductive Amination of 5-Formyl-2'-Deoxyuridine

Elzbieta Sochacka[a]; Damian Smuga[a]
[a] Institute of Organic Chemistry, Technical University of Lodz, Lodz, Poland

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NOVEL ENAMINE DERIVATIVES OF 5,6-DIHYDRO-2′-DEOXYURIDINE FORMED IN REDUCTIVE AMINATION OF 5-FORMYL-2′-DEOXYURIDINE

Elzbieta Sochacka and Damian Smuga

Institute of Organic Chemistry, Technical University of Lodz, Lodz, Poland

□ *Reductive amination of 5-formyl-3′,5′-di-O-acetyl-2′-deoxyuridine with primary amines and sodium triacetoxyborohydride ($NaBH(OAc)_3$) afforded novel enamine derivatives of 5,6-dihydro-2′-deoxyuridine as a result of unexpected 1,4-conjugate reduction of intermediate Schiff bases in addition to the secondary amine derivatives of 2′-deoxyuridine, typical 1,2-reduction products.*

Keywords Modified nucleosides; 5-formyl-2′-deoxyuridine; reductive amination; nucleoside Schiff bases; sodium triacetoxyborohydride

INTRODUCTION

Reductive amination of aldehydes and ketones is widely used in organic synthesis[1] and provides expedient access to structurally diverse amines. In general, the reductive amination is a two-step transformation which proceeds via imine intermediate, further reduced to the corresponding amine by a variety of reducing agents, including $NaBH_4$,[2] $NaBH_3CN$,[3] and $NaBH(OAc)_3$.[4–6]

Recently, reductive amination has found wide application in the synthesis of various modified nucleosides and nucleic acid conjugates.[7] In particular, reductive amination of 5-formyl-2′-deoxyuridine (f^5dU) has been used in the synthesis of 5-alkylamino derivatives of pyrimidine nucleosides.[8–11] These types of amino-modified nucleosides are useful units for nucleic acids labeling, stabilization of nucleic acids structures and for introduction of additional functionality to nucleic acid fragments designed as aptamers,

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Address correspondence to Elzbieta Sochacka, Institute of Organic Chemistry, Technical University of Lodz, Zeromskiego 116, 90-924, Lodz, Poland. E-mail: ejsochac@p.lodz.pl

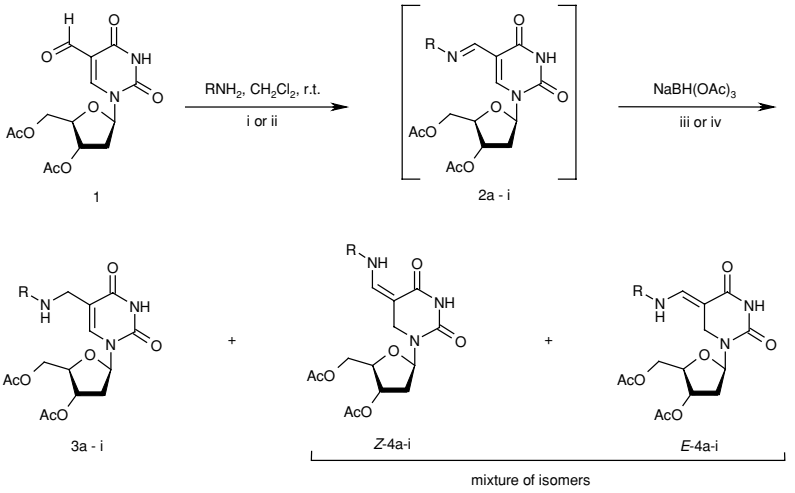
biosensors or catalysts.[12,13] In all previously reported reductive aminations of 5-formyl-2′-deoxyuridine,[8–11] $NaBH_4$, and $NaBH_3CN$ were used as the reducing agents.

In this article, we present the first application of a very mild and nontoxic sodium triacetoxyborohydride for the reductive amination of 5-formyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine. A direct reductive amination was applied for the reactions carried out in the presence of reactive primary alkyl amines and a stepwise protocol was used for the less nucleophilic aromatic amines, according to recently described protocol for the formation of Schiff bases derived from 5-formyl-2′-deoxyuridine.[14]

RESULTS AND DISCUSSION

We started experiments using 5-formyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine (**1**)[15] and *n*-butylamine as a model primary amine of high nucleophilicity ($pK_a = 10.7$). The reaction was carried out by mixing of aldehyde **1** with 1.2 equivalents of *n*-butylamine in anhydrous CH_2Cl_2 followed by addition of $NaBH(OAc)_3$ (1.2 equivalent) and additional portion (0.5 equivalent) after 2 hours (Scheme 1).

After 4 hours at room temperature, TLC analysis (silica gel, $CHCl_3$/MeOH, 9:1 *v*/*v*) showed complete disappearance of starting nucleoside **1**, with no detectable reduction of 5-formyl group as compared with



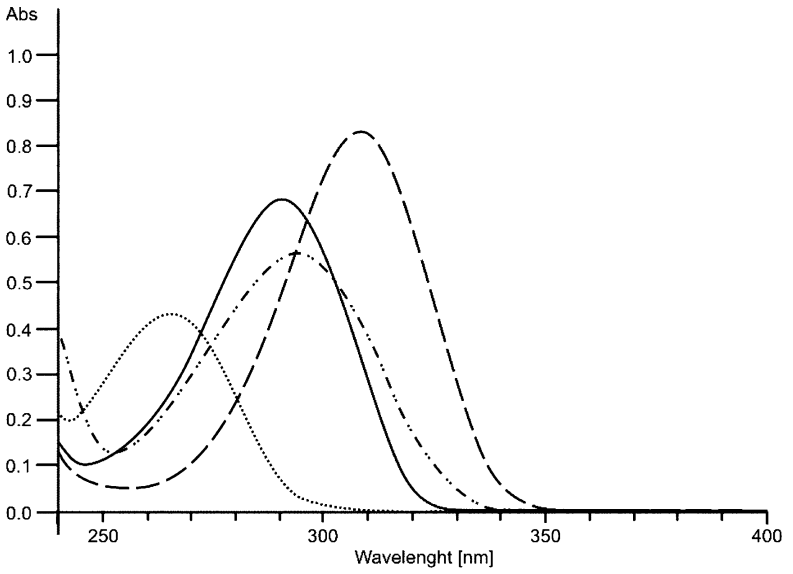
Aliphatic RNH_2 : **a**) *n*-butylamine, **b**) methylamine, **c**) histamine monomethoxytritylated at imidazole ring, **d**) benzylamine, **e**) *t*-butylamine
Aromatic RNH_2 : **f**) aniline, **g**) *p*-toluidine, **h**) *p*-nitroaniline

SCHEME 1 Reductive amination of 5-formyl-5′,3′-di-*O*-acetyl-2′-deoxyuridine (**1**) with RNH_2 **a–h** and $NaBH(OAc)_3$. *Reagents and conditions*: (i) 1.2 equivalent of RNH_2 **a–d** or (ii) 1.5 equivalent of RNH_2 **e-h**, and 2 hours for imine formation; (iii) for RNH_2 **a–d**—1.2 equivalent of $NaBH(OAc)_3$ and additional 0.5 equivalent after 2 hours, overall reaction time 4h or (iv) for RNH_2 **e–h**—1.2 equivalent of $NaBH(OAc)_3$ and additional 0.5 equivalent added after 2 hours and 4 hours, overall reaction time 16 hours.

authentic sample of 5-hydroxymethyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine.[15] We observed formation of one product of low chromatographic mobility (R_f = 0.16, strong spot, UV lamp detection at 254 nm) and two more lipophilic compounds producing very weak TLC spots (R_f = 0.44 and R_f = 0.55). The latter products were better visualized with a ninhydrin test. The polar product was easily isolated by silica gel column chromatography in 44% yield and its spectral analysis (FAB MS, ^{1}H and ^{13}C NMR data) fully confirmed the structure of expected secondary amine derivative **3a**.

However, several attempts at chromatographic separation of two more lipophilic compounds were unsuccessful and they were isolated as a mixture in 48% yield. Spectral analysis of this mixture (FAB MS, ^{1}H, and ^{13}C NMR) revealed that these compounds are *Z* and *E* isomers of the 5-butylaminomethylidene-5,6-dihydro-3′,5′-di-*O*-acetyl-2′-deoxyuridine ***Z*-4a** and ***E*-4a** (Scheme 1).

In the FAB MS, the measured *m/z* values for $[M+H]^+$ and $[M-H]^-$ were consistent with the MW calculated for **4a**. The UV spectrum of isomers **4a** (Figure 1) confirmed substantial changes in the structure of heterobase



derivative	line	λ_{max} (ε)	λ_{min}
1	———	290.5 (14000)	240.5
2a	— ·· —	295.5 (11200)	253.0
3a	-------	265.5 (8600)	243.5
***Z* and *E* 4a**	— — —	308.5 (16500)	257.0

FIGURE 1 UV spectra of **1** and **2a–4a** in $CHCl_3$, $c = 5.0 \times 10^{-5}$ mol/dm^3.

moiety as compared to **3a**. The values $\lambda_{max} = 308.5$ nm and $\lambda_{min} = 257.0$ nm explain poor visualization of TLC spots of **4a** under UV detection at 254 nm.

In a ^{1}H NMR spectrum recorded for the mixture of **4a** in the $CDCl_3$ solution, the shape of signals of H-1′ anomeric protons revealed predominance of one isomer. The ratio of the isomers (80:20) and their *Z/E* configuration were determined by the analysis of the proton signals for characteristic C=CH-NH fragment of the enamine **4a**. A doublet of higher intensity of a vinyl proton at 6.70 ppm compared to less intensive doublet of the more deshielded vinyl proton at 7.49 ppm indicated the *Z* configuration of the major isomer of **4a**. Additionally, a high chemical shift (8.37 ppm) of NH proton of major *Z* isomer may be explained in terms of intramolecular H-bonding between NH proton and oxygen atom of C-4 carbonyl group. Analogous NH signal of the minor *E* isomer was observed at 5.36 ppm. Both isomers showed a characteristic *trans*-vicinal coupling 13–14 Hz between the olefinic and the amino proton.

The formation of almost equal amounts of **3a** and **4a** can be explained by nonselective reduction of conjugated double bonds of Schiff base **2a** with $NaBH(OAc)_3$. The secondary amine derivative **3a** is a 1,2-reduction product of **2a**, while isomers ***Z/E*-4a** result from unexpected 1,4-reduction of the imine derivative. It is worth to emphasize that the 5,6-dihydrouridines **4a** are non-aromatic compounds and therefore the process of 1,4-reduction should be rather not favorable. In particular, the 1,4-reductive amination products are not observed for various aromatic aldehydes under similar reductive amination conditions with $NaBH(OAc)_3$.[4–6] In the case of 5-formyl-2′-deoxyuridine **1**, the formation of 1,4-conjugated product is probably possible due to the stabilization of dihydrouridine derivative by intramolecular hydrogen bonding. Similar effect of the intramolecular H-bonding was observed for many compounds with analogous enaminone functionality, for example, in the products derived from reactions of 3-formylchromones with amino compounds[16] and for 6-aminomethylene derivatives of 5-oxo-2-phenyl-5,6,7,8-tetrahydroquinazoline.[17]

Although the reduction with $NaBH(OAc)_3$ is not selective toward conjugated double bond system of **2a**, it is worth to mention that the transformation of aldehyde **1** to amino-modified nucleosides **3** and **4** is almost quantitative. To the best of our knowledge, the dihydrouridine derivative of **4a** structure has not been described in the literature to date. In all the reported reactions of the reductive amination of f^{5}dU, employing various amine components and $NaBH_4$ or $NaBH_3CN$, the secondary amine derivatives of 2′-deoxyuridines were the only isolated amino-modified products.[6–10,14]

The scope of f^{5}dU reductive amination carried out with $NaBH(OAc)_3$ was investigated with a series of primary amines of different nucleophilicity

TABLE 1 Yields of secondary amine 2′-deoxyuridine derivatives **3** and 5,6-dihydro-2′-deoxyuridine derivatives **4** (*Z* and *E* isomers) in reductive amination of **1** with $NaBH(OAc)_3$

Entry	Amine	% of **3**	% of **4** (*Z*/*E* ratio)[a]
a	*n*-butylamine	44	48 (80:20)
b	methylamine	39	56 (90:10)
c	histamine[b]	55	41 (85:15)
d	benzylamine	58	39 (55:45)
e	*t*-butylamine	7	85 (80:20)
f	aniline[c]	63	11 (70:30)
g	*p*-toluidine[c]	68	15 (90:10)
h	*p*-nitroaniline[d]	71	6 (90:10)

[a]Isomers ratio was determined from the ^1H NMR spectra ($CDCl_3$) of isolated **4**.

[b]The histamine derivative with MMTr on the imidazole ring was used as the amine component.

[c]Unreacted aldehyde **1** was isolated in 13% and 10% from the reaction mixture with aniline and *p*-toluidine, respectively.

[d]5-hydroxymethyl-3′,5′-di-*O*-acetyl-2′-deoxyuridine was isolated in 17% yield (product of aldehyde **1** reduction).

(aliphatic and aromatic amines), steric hindrance (*t*-butylamine) and with additional functionality present (histamine; Table 1).

The reactions of f^5dU **1** with reactive primary amines (Table 1, entries a through d) were performed following direct procedure with 1.2 molar excess of amine over aldehyde **1** and 1.7 molar equivalents of $NaBH(OAc)_3$ (1.2 equivalent of $NaBH(OAc)_3$ added directly after substrates mixing and additional 0.5 equivalent after 2 hours, Scheme 1). After 4 hours the substrate **1** was fully converted to the mixture of the corresponding products **3** and **4**, with no detectable aldehyde reduction. In experiments with *n*-butylamine and methylamine (entries a, b) the corresponding 5,6-dihydro-2′-deoxyuridine derivatives **4a** and **4b** were isolated in a slight excess over derivatives **3a** and **3b**, while for histamine and benzylamine (entries c, d) the yields of **3c** and **3d** were slightly higher than for **4c** and **4d**.

However, the predominant formation of dihydrouridine **4e** for bulky *t*-butylamine (entry e, 85% isolated yield of **4e** compared to 7% for **3e**) suggests the influence of steric factors associated with intermediate imine **2e** on the outcome of the reaction.

The reductive amination with weakly nucleophilic aromatic amines (Table 1, entries f through h) was performed according to a two-step preparative procedure with 1.5 molar excess of amine and 2 hours formation of intermediate imine. To each of the corresponding pre-formed Schiff bases **2f**–**h**, the 2.2 equivalents of $NaBH(OAc)_3$ were added in three portions (Scheme 1) and the reactions were continued for 16 hours. In the experiments with aniline and *p*-toluidine (entries f, g) the reduction

of intermediate imines with $NaBH(OAc)_3$ was not completed and the unreacted **1** was isolated in ca. 10%. No competing aldehyde reduction was observed. In the case of the least basic *p*-nitroaniline the formation of imine **2h** was not quantitative and the product of aldehyde **1** reduction (5-hydroxymethyl-2′-deoxyuridine derivative) was isolated in 17% yield. In all experiments with aromatic amines, corresponding 5-arylaminomethyl-2′-deoxyuridines **3f-h** were isolated as the major products.

CONCLUSION

We have found that $NaBH(OAc)_3$ is an efficient reducing agent towards the unique conjugate bond system of intermediate Schiff bases derived from 5-formyl-2′-deoxyuridine and various amines. In direct reductive amination of f^5dU with strong nucleophilic primary alkyl amines a quantitative conversion to amino-modified nucleosides was observed without any detectable amount of substrate aldehyde **1** reduction. For the non-hindered amine components, the reductive amination of **1** afforded nearly the same amounts of 1,2-reduction product **3** (2′-deoxyuridine derivatives) and of 1,4-reduction (**4**, 5,6-dihydro-2′-deoxyuridine analogs). For bulky *t*-butylamine, the predominant formation of the 5,6-dihydrouridine derivative (isolated yield 85%) indicates the influence of steric factors on the reduction process. In the reductive amination of aldehyde **1** with aromatic amines the corresponding secondary amine derivatives of 2′-deoxyuridine were isolated in good yields as the main reaction products. The new enamine analogs **4** are in fact nucleosides with vinylogous amide functionality which can explain their relatively high stability.

Our results expand the knowledge about reductive amination of f^5dU and may be useful in designing and synthesis of novel 5-amino-modified nucleosides for structural and biological activity studies.

EXPERIMENTAL

Representative Procedure for the Direct Reductive Amination of 1; Reaction with *n*-Butylamine

5-Formyl-5′,3′-di-O-acetyl-2′-deoxyuridine (**1**) (340 mg, 1 mmol) was dried by repeated co-evaporation with anhydrous CH_2Cl_2 (2 × 10 mL) and finally dissolved in the same solvent (7 mL). To this stirred solution, *n*—butylamine (118 μL 1.2 mmol) was added followed by immediate addition of $NaBH(OAc)_3$ (254 mg, 1.2 mmol). After 2 hours at room temperature, when TLC analysis ($CHCl_3$/MeOH–9:1, v/v system) revealed some remaining aldehyde **1**, the second portion of $NaBH(OAc)_3$ (106 mg, 0.5 mmol) was added. After stirring for an additional 2 hours, the reaction was quenched with $NaHCO_3$ (10 mL, 5% aq. solution) and then extracted with

CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried ($MgSO_4$), filtered and concentrated in vacuo. The oily residue was chromatographed on a silica gel column with increasing amounts (from 0 to 25%) of CH_3OH in $CHCl_3$. The corresponding fractions (checked on TLC with ninhydrine test) were collected and evaporated to give 5-*n*-butylaminomethylidene-5,6-dihydro-5′,3′-di-*O*-acetyl-2′-deoxyuridine (**4a)** as a mixture of *Z* and *E* isomers (190 mg, yield 48%) and 5-*n*-butylaminomethyl-5′,3′-di-*O*-acetyl-2′-deoxyuridine (**3a**) (175 mg, yield 44%).

TLC (silica gel plates): **3a** R_f 0.16 and **4a** R_f 0.44, 0.55 ($CHCl_3$/MeOH 90:10); **3a** R_f 0.10 and **4a** R_f 0.37, 0.48 (AcOEt/MeOH 95:5).

Spectral Data for 3a and 4a Z and E Isomers

3a: *m/z* (HRMS, FAB) 398.1919 ($[M+H]^+$ $C_{18}H_{28}N_3O_7$ requires 398.1927); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.95 (t, 3H, $J = 7.3$ Hz, CH_3CH$_2$), 1.32–1.50 (m, 2H, CH$_3$CH_2CH$_2$), 1.58–1.80 (m, 2H, CH$_2$ CH_2 CH$_2$), 2.11 (s, 3H, CH_3COO), 2.15 (s, 3H, CH_3COO), 2.39 (ddd, 1H, $J_{H2',H3'} = 6.4$ Hz, $J_{H2',H1v} = 8.4$ Hz, $J_{gem} = 14.6$ Hz, H2′), 2.51 (ddd, 1H, $J_{H2'',H3'} = 2.0$ Hz, $J_{H2'',H1'} = 5.9$ Hz, $J_{gem} = 14.4$ Hz, H2″), 2.75–2.97 (m, 2H, CH$_2$CH_2NH), 3.67 (d, 1H, $J_{gem} = 13.1$ Hz, one of CH_2–7), 3.74 (d, 1H, $J_{gem} = 13.1$ Hz, one of CH_2–7), 4.22 (m, 1H, H4′), 4.30 (dd, 1H, $J_{H5'',H4'} = 3.7$ Hz, $J_{gem} = 11.9$ Hz, H5″), 4.45 (dd, 1H, $J_{H5',H4'} = 5.4$ Hz, $J_{gem} = 12.0$ Hz, H5′), 5.23 (dt, 1H, $J_{H3',H2''} = J_{H3',H4'} = 2.1$ Hz, $J_{H3',H2'} = 6.5$ Hz, H3′), 6.28 (dd, 1H, $J_{H1',H2''} = 5.8$ Hz, $J_{H1',H2'} = 8.3$ Hz, H1′), 7.83 (s, 1H, H6); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.68 (*C*H$_3$CH$_2$), 20.03(CH$_3$*C*H$_2$CH$_2$), 20.89 (2x*C*H$_3$COO), 29.15 (CH$_2$*C*H$_2$CH$_2$), 36.91 (C2′), 44.31 (C7), 47.79 (CH$_2$*C*H$_2$NH), 63.85 (C5′), 74.29 (C3′), 82.49 (C4′), 85.42 (C1′), 107.57 (C5), 141.26 (C6), 150.54 (C2), 164.54 (C4), 170.31 (CH$_3$*C*OO), 170.60 (CH$_3$*C*OO);); UV ($CHCl_3$) $\lambda_{max} = 265.5$ nm ($\varepsilon = 8600$).

4a *Z* and *E* isomers; *m/z* (HRMS, FAB) 398.1938 ($[M+H]^+$ $C_{18}H_{28}N_3O_7$ requires 398.1927); ^{1}H NMR (250 MHz, $CDCl_3$) δ 0.94 (t, $J = 7.2$ Hz, 6H, CH_3CH$_2$ of *Z* and *E*), 1.24–1.47 (m, 4H, CH$_3$CH_2CH$_2$ of *Z* and *E*), 1.47–1.63 (m, 4H, CH$_2$ CH_2 CH$_2$ of *Z* and *E*), 1.98–2.26 (m, 16H, 2xCH_3COO, H2′, H2″ of *Z* and *E*), 3.20 (q, $J = 6.6$ Hz, 2H, CH$_2$CH_2NH of *Z*), 3.28 (m, 1H, CH$_2$CH_2NH of *E*), 3.53 (dd, $^4J_{H6,H7} = 1.4$ Hz, $J_{gem} =$ 13.2 Hz, 1H, one of CH_2 -6 of *E*), 3.75 (d, $J_{gem} = 12.6$ Hz, 1H, one of CH_2–6 of *Z*), 3.98 (d, $J_{gem} = 12.7$ Hz, 1H, one of CH_2–6 of *Z*), 4.00 (m, 1H, one of CH_2–6 of *E*), 4.11 (m, 1H, H4′ of *Z*), 4.15–4.38 (m, 4H, H5′, H5″ of *Z*, H4′, H5″ of *E*), 4.52 (dd, $J_{H5',H4'} = 8.8$ Hz, $J_{gem} = 12.2$ Hz, 1H, H5′ of *E*), 5.02–5.18 (m, 2H, H3′ of *Z* and *E*), 5.36 (m, 1H, CH$_2$N*H*CH of *E*), 6.32 (dd, $J_{H1',H2''} = 6.1$ Hz, $J_{H1',H2'} = 8.7$ Hz, 1H, H1′ of *Z*), 6.41 (dd, $J_{H1',H2''} = 5.6$ Hz, $J_{H1',H2'} = 8.6$ Hz, 1H, H1′ of *E*), 6.70 (d, $J_{H7,NH} = 12.9$ Hz, 1H, H7 of *Z*), 7.10 (bs, 1H, N*H*-3 of *Z*), 7.14 (bs, 1H, N*H*-3 of *E*), 7.49 (d, $J_{H7,NH} = 13.1$ Hz, 1H, H7 of *E*), 8.37 (m, 1H, CH$_2$N*H*CH of *Z*); ^{13}C NMR (63 MHz, $CDCl_3$) δ 13.74

(CH_3CH_2 of *Z* and *E*), 19.70 ($CH_3CH_2CH_2$ of *E*), 19.76 ($CH_3CH_2CH_2$ of *E*), 20.98 (CH_3COO of *Z*), 21.05 (CH_3COO of *Z* and *E*) 21.22 (CH_3COO of *E*), 32.70 (C2′of *E*), 33.27 ($CH_2CH_2CH_2$ of *Z* and *E*, C2′ of *Z*), 36.40 (C6 of *E*), 40.27 (C6 of *Z*), 48.88 (CH_2CH_2NH of *Z*), 49.04 (CH_2CH_2NH of *E*), 64.05 (C5′ of *E*), 64.15 (C5′ of *Z*), 74.36 (C3′ of *Z* and *E*), 80.35 (C4′ of *Z*), 81.14 (C4′ of *E*), 84.18 (C1′ of *Z*), 85.00 (C1′ of *E*), 85.08 (C5 of *Z*), 87.34 (C5 of *E*), 146.70 (C7 of *E*), 149.95 (C7 of *Z*), 152.85 (C2 of *E*), 153.74 (C2 of *Z*), 165.05 (C4 of *E*), 166.98 (C4 of *Z*), 170.68 (2xCH_3COO of *Z*), 170.77 (CH_3COO- C3′of *E*), 171.62 (CH_3COO-C5′of *E*); UV ($CHCl_3$) $\lambda_{max} = 308.5$ nm ($\varepsilon = 16500$).

Direct Reductive Amination with Methylamine Hydrochloride

The same conditions were applied as for *n*-butylamine besides that methylamine hydrochloride was used and the free amine was obtained by the addition of equimolar amount of triethylamine.

Isolated products: **3b**, 138 mg, yield 39%; **4b**, 199 mg, yield 56%

TLC: **3b** R_f 0.06 and **4b** R_f 0.42, 0.58 ($CHCl_3$/MeOH 90:10); **3b** R_f 0.02 and **4b** R_f 0.29, 0.58 (AcOEt/MeOH 95:5).

Spectral Data for 3b and 4b Z and E Isomers

3b: *m/z* (HRMS, FAB) 356.1469 ($[M+H]^+$ $C_{15}H_{22}N_3O_7$ requires 356.1458); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.11 (s, 3H, C*H*$_3$COO), 2.15 (s, 3H, C*H*$_3$COO), 2.27 (ddd, $J_{H2',H3'} = 6.6$ Hz, $J_{H2',H1'} = 8.5$ Hz, $J_{gem} = 14.5$ Hz, 1H, H2′), 2.43 (ddd, $J_{H2'',H3'} = 1.9$ Hz, $J_{H2'',H1'} = 5.6$ Hz, $J_{gem} = 14.3$ Hz, 1H, H2″), 2.52 (s, 3H, C*H*$_3$NH), 3.56 (d, $J_{gem} = 13.6$ Hz, 1H, one of CH_2–7), 3.63 (d, $J_{gem} = 13.8$ Hz, 1H, one of CH_2–7), 4.23 (m, 1H, H4′), 4.31 (dd, $J_{H5'',H4'} = 3.4$ Hz, $J_{gem} = 12.0$ Hz, 1H, H5″), 4.41 (dd, $J_{H5',H4'} = 4.8$ Hz, $J_{gem} = 12.0$ Hz, 1H, H5′), 5.22 (dt, $J_{H3',H2''} = J_{H3',H4'} = 2.0$ Hz, $J_{H3',H2'} = 6.7$ Hz, 1H, H3′), 6.31 (dd, $J_{H1',H2''} = 5.6$ Hz, $J_{H1',H2'} = 8.5$ Hz, 1H, H1′), 7.66 (s, 1H, H6); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.95 (*C*H$_3$COO), 21.05 (*C*H$_3$COO), 34.55 (*C*H$_3$NH), 37.34 (C2′), 47.13 (C7), 63.99 (C5′), 74.41(C3′), 82.49 (C4′), 85.26 (C1′), 110.40 (C5′), 138.96 (C6), 150.75 (C2), 164.50 (C4), 170.52 (CH_3COO), 170.68 (CH_3COO); UV ($CHCl_3$) $\lambda_{max} =$ 265 nm ($\varepsilon = 8100$).

4b *Z* and *E* isomers; *m/z* (HRMS, FAB) 356.1474 ($[M+H]^+$ $C_{15}H_{22}N_3O_7$ requires 356.1458); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.10 (s, 3H, C*H*$_3$COO of *Z*), 2.11 (s, 3H, C*H*$_3$COO of *Z*), 2.11 (s, 3H, C*H*$_3$COO of *E*), 2.12 (s, 3H, C*H*$_3$COO of *E*), 2.00–2.28 (m, 4H, H2′, H2″ of *Z* and *E*), 3.01 (d, $J = 5.0$ Hz, 3H, C*H*$_3$NH of *Z*), 3.07 (d, $J = 4.7$ Hz, 3H, C*H*$_3$NH of *E*), 3.66 (dd, $^4J_{H6,H7} = 1.5$ Hz, $J_{gem} = 13.2$ Hz, 1H, one of C*H*$_2$ -*6* of *E*), 3.79 (d, $J_{gem} = 12.6$ Hz, 1H, one of C*H*$_2$–6 of *Z*), 3.94 (d, $J_{gem} = 12.5$ Hz, 1H, one of C*H*$_2$–6 of *Z*), 3.98 (dd, $^4J_{H6,H7} = 1.3$ Hz, 1H, $J_{gem} = 13.0$ Hz, one of C*H*$_2$ -*6* of *E*), 4.06–4.28 (m, 5H, H4′ of *Z* and *E*, H5′, H5″ of *Z*, H5″ of *E*), 4.51

(dd, $J_{H5',H4'} = 8.8$ Hz, $J_{gem} = 12.2$ Hz, 1H, H5′ of *E*), 5.05–5.14 (m, 2H, H3′ of *Z* and *E*), 5.25 (m, 1H, CH_3NH of *E*), 6.32 (dd, $J_{H1',H2''} = 6.1$ Hz, $J_{H1',H2'} = 8.7$ Hz, 1H, H1′ of *Z*), 6.40 (dd, $J_{H1',H2''} = 5.7$ Hz, $J_{H1',H2'} = 9.1$ Hz, 1H, H1′ of *E*), 6.68 (d, $J_{H7,NH} = 13.1$ Hz, 1H, H7 of *Z*), 7.31 (s, 1H, N*H*-3 of *Z*), 7.34 (s, 1H, N*H*-3 of *E*), 7.45 (dt, $^4J_{H7,H6} = 1.3$ Hz, 1H, $J_{H7,NH} = 14.4$ Hz, H7 of *E*), 8.22 (m, 1H, CH_3NH of *Z*); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.04 (CH_3COO of *Z* and *E*), 21.10 (CH_3COO of *Z* and *E*), 33.40 (CH_3NH of *Z* and *E*), 35.37 (C2′ of *Z* and *E*), 36.25 (C6 of *E*), 40.30 (C6 of *Z*), 64.10 (C5′ of *E*), 64.21 (C5′ of *Z*), 74.40 (C3′ of *Z* and *E*), 80.43 (C4′ of *Z*), 81.19 (C4′ of *E*), 84.23 (C1′ of *Z*), 85.05 (C1′ of *E*), 85.59 (C5 of *Z*), 87.94 (C5 of *E*), 147.62 (C7 of *E*), 151.07 (C7 of *Z*), 152.80 (C2 of *E*), 153.64 (C2 of *Z*), 164.99 (C4 of *E*), 167.03 (C4 of *Z*), 170.71 (CH_3COO of *Z* and *E*), 170.79 (CH_3COO of *Z* and *E*); UV ($CHCl_3$) $\lambda_{max} = 305$ nm ($\varepsilon = 13000$).

Direct Reductive Amination with Histamine Derivative

The histamine derivative with MMTr on the imidazole ring was prepared according to the procedure described by Verbeure, B., *at al.*[18]

Isolated products: **3c**, 390 mg, yield 55%; **4c**, 290 mg, yield 41%.

TLC: **3c** R_f 0.32 and **4c** R_f 0.48, 0.63 ($CHCl_3$/MeOH 90:10); **3c** R_f 0.11 and **4c** R_f 0.23, 0.41 (AcOEt/MeOH 90:10).

Spectral Data for 3c and 4c Z and E Isomers

3c: *m/z* (HRMS, FAB) 708.3052 ($[M+H]^+$ $C_{39}H_{42}N_5O_8$ requires 708.3033); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.10 (s, 3H, CH_3COO), 2.11 (s, 3H, CH_3COO), 2.30 (ddd, $J_{H2',H3'} = 6.4$ Hz, $J_{H2',H1'} = 8.4$ Hz, $J_{gem} = 14.5$ Hz, 1H, H2′), 2.43 (ddd, $J_{H2'',H3'} = 1.8$ Hz, $J_{H2'',H1'} = 5.7$ Hz, $J_{gem} = 14.3$ Hz, 1H, H2″), 2.80 (t, $J = 7.0$ Hz, 2H, $ImCH_2$), 2.99 (t, $J = 7.0$ Hz, 2H, CH_2NH), 3.57 (d, $J_{gem} = 13.7$ Hz, 1H, one of CH_2–7), 3.66 (d, $J_{gem} = 13.8$ Hz, 1H, one of CH_2–7), 3.81 (s, 3H, OCH_3), 4.21 (m, 1H, H4′), 4.28 (dd, $J_{H5'',H4'} = 3.5$ Hz, $J_{gem} = 12.0$ Hz, 1H, H5″), 4.39 (dd, $J_{H5',H4'} = 4.7$ Hz, $J_{gem} = 12.0$ Hz, 1H, H5′), 5.22 (dt, $J_{H3',H2''} = J_{H3',H4'} = 2.0$ Hz, $J_{H3',H2'} = 6.3$ Hz, 1H, H3′), 6.30 (dd, $J_{H1',H2''} = 5.7$ Hz, $J_{H1',H2'} = 8.6$ Hz, 1H, H1′), 6.59 (d, $^4J_{H5,H2} = 1.2$ Hz, 1H, Im-C*H*-5), 6.77–7.37 (m, 14H, MMTr), 7.38 (d, $^4J_{H2,H5} = 1.4$ Hz, 1H, Im-C*H*-2), 7.66 (s, 1H, H6); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.08 (2xCH_3COO), 27.56 ($ImCH_2$), 37.34 (C2′), 45.52 (C7), 48.85 (CH_2NH), 55.47 (OCH_3), 64.03 (C5′), 74.58 (MMTr-CPh_3), 75.05 (C3′), 82.52 (C4′), 85.30 (C1′), 111.73 (C5), 113.45(MMTr-o′), 118.74(Im-*C*H-5), 128.19 (MMTr-o,p), 129.82 (MMTr-m), 131.30 (MMTr-m′), 134.64 (Im-*C*H-4), 138.13 (MMTr-i′), 138.64 (C6),138.71 (Im-*C*H-2), 142.88 (MMTr-i), 150.43 (C2), 159.25 (MMTr-p′), 163.47 (C4), 170.51 (CH_3COO), 170.65 (CH_3COO); UV ($CHCl_3$) $\lambda_{max} = 266$ nm ($\varepsilon = 7700$).

4c *Z* and *E* isomers; *m/z* (HRMS, FAB) 708.3048 ($[M+H]^+$ $C_{39}H_{42}N_5O_8$ requires 708.3033 ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.08 (s, 3H, C*H*$_3$COO of *Z*), 2.09 (s, 3H, C*H*$_3$COO of *Z*), 2.03–2.19 (m, 10H, 2xC*H*$_3$COO of *E*, H2′, H2″ of *Z* and *E*), 2.77 (t, J = 6.7 Hz, 2H, ImC*H*$_2$ of *Z*), 2.79–2.88 (m, 2H, ImC*H*$_2$ of *E*), 3.48–3.60 (m, 4H, C*H*$_2$NH of *Z* and *E*), 3.81 (s, 3H, OC*H*$_3$ of *Z*), 3.82 (s, 3H, OC*H*$_3$ of *E*), 3.68–3.98 (m, 4H, C*H*$_2$–6 of *Z* and *E*), 3.99–4.39 (m, 6H, H4′, H5′, H5″ of *Z* and *E*), 5.06–5.19 (m, 3H, H3′ of *Z* and *E*, CH_2N*H*CH of *E*), 6.30 (dd, $J_{H1',H2''}$ = 5.9 Hz, $J_{H1',H2'}$ = 8.9 Hz, 1H, H1′ of *Z*), 6.41 (dd, $J_{H1',H2''}$ = 5.9 Hz, $J_{H1',H2'}$ = 8.8 Hz, 1H, H1′ of *E*), 6.60 (d, $^4J_{H5,H2}$ = 1.0 Hz, 1H, Im-C*H*-5 of *Z*), 6.61 (d, $^4J_{H5,H2}$ = 1.0 Hz, 1H, Im-C*H*-5 of *E*), 6.70 (d, $J_{H7,NH}$ = 13.1 Hz, 1H, H7 of *Z*), 6.79–7.41 (m, 31H, MMTr, N*H*-3 of *Z* and *E*, Im-C*H*-2 of *E*), 7.43 (d, $^4J_{H2,H5}$ = 1.3 Hz, 1H, Im-C*H*-2 of *Z*), 7.46 (m, 1H, H7 of *E*), 8.43 (m, 1H, CH_2N*H*CH of *Z*); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.00 (*C*H$_3$COO of *E* and *Z*), 21.06 (*C*H$_3$COO of *E* and *Z*), 28.90 (Im*C*H$_2$ of *E*), 30.09 (Im*C*H$_2$ of *Z*), 32.69 (C2′of *E*), 33.30 (C2′ of *Z*), 36.84 (C6 of *E*), 40.32 (C6 of *Z*), 48.75 (*C*H$_2$NH of *Z*), 49.34 (*C*H$_2$NH of *E*), 55.42 (OCH$_3$ of *Z* and *E*), 63.94 (C5′ of *E*), 64.16 (C5′ of *Z*), 74.34 (C3′ of *E*), 74.46 (C3′ of *Z*), 75.10 (MMTr-CPh$_3$ of *Z*), 75.22 (MMTr-CPh$_3$ of *E*), 80.44 (C4′of *Z*), 80.66 (C4′ of *E*), 84.20 (C1′ of *Z*), 84.59 (C1′ of *E*), 85.00 (C5 of *Z*), 87.43 (C5 of *Z*), 113.44 (MMtr-o′ of *Z* and *E*), 118.91 (Im-*C*H-5 of *E*), 119.60 (Im-*C*H-5 of *Z*), 128.17 (MMTr-o of *Z* and *E*, MMTr-p of *Z*), 128.44 (MMTr-p of *E*), 129.74 (MMTr-m of *Z* and *E*), 131.23 131.30 (MMTr-m′of *Z* and *E*), 134.31 (Im-*C*H-4 of *E*), 134.43 (Im-*C*H-4 of *Z*), 137.18 (MMTr-i′ of *Z*), 137.75 (MMTr-i′ of *E*), 138.57 (Im-*C*H-2 of *E*), 138.83 (Im-*C*H-2 of *Z*), 142.61 (MMTr-i of *E*), 142.70 (MMTr-i of *Z*), 146.72 (C7 of *E*), 150.15 (C7 of *Z*), 153.09 (C2 of *E*), 153.81 (C2 of *Z*), 159.25 (MMTr-p′ of *Z* and *E*), 164.91 (C4 of *E*), 166.71 (C4 of *Z*), 170.63 (CH$_3$*C*OO of *Z* and *E*), 171.09 (CH$_3$*C*OO of *Z* and *E*); UV ($CHCl_3$) λ_{max} = 305 nm (ε = 12600).

Direct Reductive Amination with Benzylamine

Isolated products: **3d**, 250 mg, yield 58%; **4d**, 168 mg, yield 39%.

TLC: **3d** R_f 0.23 and **4d** R_f 0.30, 0.49 ($CHCl_3$/MeOH 95:5); **3d** R_f 0.25 and **4d** R_f 0.30, 0.56 (AcOEt/MeOH 95:5).

Spectral Data for 3d and 4d Z and E Isomers

3d: *m/z* (HRMS, FAB) 432.1764 ($[M+H]^+$ $C_{21}H_{26}N_3O_7$ requires 432.1771); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.98 (s, 3H, C*H*$_3$COO), 2.11 (s, 3H, C*H*$_3$COO), 2.17 (m, 1H, H2′), 2.45 (ddd, $J_{H2'',H3'}$ = 1.8 Hz, $J_{H2'',H1'}$ = 5.6 Hz, J_{gem} = 14.1 Hz, 1H, H2″), 3.52 (s, 2H, C*H*$_2$–7), 3.80 (s, 2H, PhC*H*$_2$), 4.20–4.32 (m, 2H, H4′, H5″), 4.38 (dd, $J_{H5',H4'}$ = 4.0 Hz, J_{gem} = 11.8 Hz, 1H, H5′), 5.20 (dt, $J_{H3',H2''}$ = $J_{H3',H4'}$ = 1.8 Hz, $J_{H3',H2'}$ = 6.5 Hz, 1H, H3′), 6.33 (dd, $J_{H1',H2''}$ = 5.5 Hz, $J_{H1',H2'}$ = 8.6 Hz, 1H, H1′), 7.18–7.38 (m, 6H,

Ph), 7.46 (s, 1H, H6); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.82 (CH_3COO), 21.05 (CH_3COO), 37.62 (C2′), 45.62 (C7), 53.21 ($PhCH_2$), 64.01 (C5′), 74.37 (C3′), 82.36 (C4′), 85.04 (C1′), 113.61 (C5), 127.33 (Ph-p), 128.35 (Ph-m), 128.65 (Ph-o), 136.42 (C6), 139.61 (Ph-i), 150.51 (C2), 163.52 (C4), 170.46 (CH_3COO), 170.54 (CH_3COO); UV ($CHCl_3$) $\lambda_{max} = 264$ nm ($\varepsilon = 8200$).

4d *Z* and *E* isomers; *m/z* (HRMS, FAB) 432.1755 ($[M+H]^+$ $C_{21}H_{26}N_3O_7$ requires 432.1771); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.05 (s, 3H, CH_3COO of *Z*), 2.09 (s, 3H, CH_3COO of *Z*), 1.94–2.39 (m, 10H, 2xCH_3COO of *E*, H2′, H2″ of *Z* and *E*), 3.67 (dd, $^4J_{H6,H7} = 1.8$ Hz, $J_{gem} = 13.2$ Hz, 1H, one of CH_2 -6 of *E*), 3.79 (d, $J_{gem} = 12.8$ Hz, 1H, one of CH_2–6 of *Z*), 3.95 (d, $J_{gem} = 12.8$ Hz, 1H, one of CH_2–6 of *Z*), 4.01 (m, 1H, one of CH_2 *-6* of *E*), 4.10 (m, 1H, H4′ of *Z*), 4.21–4.56 (m, 5H, H5′, H5″ of *Z* and *E*, H4′ of *E*), 4.39 (d, $J = 5.9$ Hz, 2H, $PhCH_2NH$ of *Z*), 4.44 (d, $J = 5.8$ Hz, 1H, $PhCH_2NH$ of *E*), 5.03–5.14 (m, 2H, H3′ of *Z* and *E*), 5.75 (m, 1H, CH_2NHCH of *E*), 6.32 (dd, $J_{H1',H2''} = 6.1$ Hz, $J_{H1',H2'} = 8.7$ Hz, 1H, H1′ of *Z*), 6.40 (dd, $J_{H1',H2''} = 5.6$ Hz, $J_{H1',H2'} = 9.5$ Hz, 1H, H1′ of *E*), 6.76 (d, $J_{H7,NH} = 12.9$ Hz, 1H, H7 of *Z*), 7.11–7.46 (m, 12H, Ph, N*H*-3 of *Z* and *E*), 7.60 (dt, $^4J_{H7,H6} = 1.4$ Hz, $J_{H7,NH} = 14.3$ Hz, 1H, H7 of *E*), 8.68 (m, 1H, CH_2NHCH of *Z*); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.99 (2xCH_3COO of *E*), 21.10 (2xCH_3COO of *Z*), 32.71(C2′of *E*), 33.37 (C2′ of *Z*), 36.42 (C6 of *E*), 40.32 (C6 of *Z*), 52.48 ($PhCH_2$ of *Z*), 53.19 ($PhCH_2$ of *E*), 64.05 (C5′ of *E*), 64.16 (C5′ of *Z*), 74.37 (C3′ of *Z* and *E*), 80.45 (C4′of *Z*), 81.32 (C4′ of *E*), 84.24 (C1′ of *Z*), 85.13 (C1′ of *E*), 86.54 (C5 of *Z*), 88.48 (C5 of *E*), 127.41 (Ph-o of *Z*), 127.73 (Ph-o of *E*), 128.02 (Ph-p of *E*), 128.12 (Ph-p of *E*), 129.03 (Ph-m of *Z* and *E*), 137.87 (Ph-i of *E*), 138.07 (Ph-i of *Z*), 146.35 (C7 of *E*), 149.54 (C7 of *Z*), 152.67 (C2 of *E*), 153.55 (C2 of *Z*), 165.00 (C4 of *E*), 166.96 (C4 of *Z*), 170.69 (CH_3COO of *Z* and *E*), 170.77 (CH_3COO of *Z* and *E*); UV ($CHCl_3$) $\lambda_{max} = 304.5$ nm ($\varepsilon = 14600$).

Representative Procedure for the Undirect Reductive Amination of 1; Reaction with *t*-Butylamine

5-Formyl-5′,3′-di-O-acetyl-2′-deoxyuridine (**1**) (340 mg, 1 mmol), predried by repeated evaporation with anhydrous CH_2Cl_2 (2 × 10 mL), was dissolved in the same solvent (7 mL) and *t*-butylamine (158 μL 1.5 mmol) was added. The reaction mixture was stirred for 2 hours at room temperature and then treated with $NaBH(OAc)_3$ (254 mg, 1.2 mmol). After 2 and 4 hours, when TLC analysis ($CHCl_3$/MeOH–95:5, v/v system) revealed some remaining aldehyde **1**, two additional portions of $NaBH(OAc)_3$ (each 106 mg, 0.5 mmol) were added. After stirring for the next 12 hours, the reaction was quenched with $NaHCO_3$ (10 mL, 5% aq. solution) and then extracted with CH_2Cl_2 (3 × 20 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The oily residue was purified on

a silica gel column using increasing amounts of CH_3OH in $CHCl_3$ (from 0 to 25%). The corresponding fractions (checked on TLC with ninhydrine test) were collected and evaporated to give 5-*t*-butylaminomethylidene-5, 6-dihydro-5′,3′-di-*O*-acetyl-2′-deoxyuridine (**4e)** as a mixture of *Z* and *E* isomers (337 mg, yield 85%) and 5-*t*-butylaminomethyl-5′,3′-di-*O*-acetyl-2′-deoxyuridine (**3e**) (28 mg, yield 7%).

TLC: **3e** R_f 0.09 and **4e** R_f 0.20, 0.28 in ($CHCl_3$/MeOH 95:5); **3e** R_f 0.03 and **4e** R_f 0.28, 0.58 (AcOEt/MeOH 95:5).

Spectral Data for 3e and 4e Z and E Isomers

3e: *m/z* (HRMS, FAB) 398.1909 ($[M+H]^+$ $C_{18}H_{28}N_3O_7$ requires 398.1927); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.43 (s, 9H, $(CH_3)_3C$), 2.11 (s, 3H, CH_3COO), 2.20 (s, 3H, CH_3COO), 2.50–2.73 (m, 2H, H2′, H2″), 3.63 (d, $J_{gem} = 12.5$ Hz, 1H, one of CH_2–7), 3.82 (d, $J_{gem} = 12.3$ Hz, 1H, one of CH_2–7), 4.20 (ddd, $J_{H4',H3'} = 2.0$ Hz, $J_{H4',H5''} = 3.3$ Hz, $J_{H4',H5'} = 5.5$ Hz, 1H, H4′), 4.29 (dd, $J_{H5'',H4'} = 3.4$ Hz, $J_{gem} = 12.0$ Hz, 1H, H5″), 4.55 (dd, $J_{H5',H4'} = 5.5$ Hz, $J_{gem} = 11.9$ Hz, 1H, H5′), 5.26 (m, 1H, H3′), 6.31 (m, 1H, H1′), 7.98 (s, 1H, H6);

^{13}C NMR (63 MHz, CDCl3) δ 21.12 (CH_3COO), 21.30 (CH_3COO), 26.76 ($(CH_3)_3C$), 37.04 (C2′), 38.57 (C7), 55.87 ($(CH_3)_3C$), 64.19 (C5′), 74.85 (C3′), 83.36 (C4′), 85.88 (C1′), 105.11 (C5), 144.06 (C6), 149.70 (C2), 164.82 (C4), 170.57(CH_3COO), 170.98 (CH_3COO); UV ($CHCl_3$) $\lambda_{max} =$ 266 nm ($\varepsilon = 7900$).

4e *Z* and *E* isomers; *m/z* (HRMS, FAB) 398.1919 ($[M+H]^+$ $C_{18}H_{28}N_3O_7$ requires 398.1927); ^{1}H NMR (250 MHz, $CDCl_3$) δ 1.31 (s, 18H, $(CH_3)_3C$ of *Z*), 1.34 (s, 3H, $(CH_3)_3C$ of *E*), 2.10 (s, 3H, CH_3COO of *Z*), 2.11 (m, 3H, CH_3COO of *Z*), 2.12 (m, 3H, CH_3COO of *E*), 2.13 (s, 3H, CH_3COO of *E*), 2.01–2.31 (m, 4H, H2′, H2″ of *Z* and *E*), 3.64 (dd, $^4J_{H6,H7} = 1.6$ Hz, $J_{gem} =$ 13.2 Hz, 1H, one of CH_2 -6 of *E*), 3.80 (dd, $^4J_{H6,H7} = 0.8$ Hz, $J_{gem} = 12.6$ Hz, 1H, one of CH_2–6 of *Z*), 3.96 (dd, $^4J_{H6,H7} = 0.8$ Hz, $J_{gem} = 12.6$ Hz, 1H, one of CH_2–6 of *Z*), 4.00 (dd, $^4J_{H6\cdot H7} = 1.4$ Hz, $J_{gem} = 13.3$ Hz, 1H, one of CH_2 -6 of *E*), 4.11 (m, 1H, H4′ of *Z*), 4.16–4.44 (m, 4H, H5′, H5″ of *Z*, H4′, H5″ of *E*), 4.53 (dd, $J_{H5',H4'} = 1.8$ Hz, $J_{gem} = 9.1$ Hz, 1H, H5′ of *E*), 5.02–5.18 (m, 2H, H3′ of *Z* and *E*), 5.45 (d, $J_{NH,H7} = 15.0$ Hz, 1H, CN*H*CH of *E*), 6.34 (dd, $J_{H1',H2''} = 6.0$ Hz, $J_{H1',H2'} = 8.8$ Hz, 1H, H1′ of *Z*), 6.41 (dd, $J_{H1',H2''} = 5.6$ Hz, $J_{H1',H2'} = 9.2$ Hz, 1H, H1′ of *E*), 6.88 (d, $J_{H7,NH} = 13.6$ Hz, 1H, H7 of *Z*), 7.16 (bs, 1H, N*H*-3 of *Z*), 7.20 (s, 1H, N*H*-3 of *E*), 7.68 (dt, $J_{H7,H6} = 1.5$ Hz, $J_{H7,NH} = 15.0$ Hz, 1H, H7 of *E*), 8.65 (d, $J_{NH,H7} = 13.6$ Hz, 1H, CN*H*CH of *Z*); ^{13}C NMR (63 MHz, $CDCl_3$) δ 21.02 (2xCH_3COO of *Z*), 21.10 (2xCH_3COO of *E*), 30.27 ($(CH_3)_3C$ of *Z* and *E*), 32.72 (C2′of *E*), 33.28 (C2′ of *Z*), 36.44 (C6 of *E*), 40.58 (C6 of *Z*), 52.32 ($(CH_3)_3C$ of *Z*), 53.22($(CH_3)_3C$ of *E*), 64.00 (C5′ of *E*), 64.14 (C5′ of *Z*), 74.36 (C3′ of *Z*), 74.47 (C3′ of *E*), 80.40 (C4′ of *Z*), 81.44 (C4′ of *E*), 84.25 (C1′ of *Z*), 84.98

(C5 of *Z*), 85.19 (C1′ of *E*), 87.55 (C5 of *E*), 142.31 (C7 of *E*), 145.65 (C7 of *Z*), 152.69 (C2 of *E*), 153.73 (C2 of *Z*), 164.80 (C4 of *E*), 166.72 (C4 of *Z*), 170.71, 170.80, 171.45 (2xCH_3COO of *Z* and *E*); UV ($CHCl_3$) $\lambda_{max} = 305$ nm ($\varepsilon = 16200$).

Undirect Reductive Amination with Aniline

Isolated products: **3f**, 263 mg, yield 63%; **4f**, 46 mg, yield 11%.

TLC: **3f** R_f 0.20 and **4f** R_f 0.41, 0.49 ($CHCl_3$/MeOH 95:5); **3f** R_f 0.60 and **4f** R_f 0.55, 0.72 (AcOEt/MeOH 95:5).

Spectral Data for 3f and 4f Z and E Isomers

3f: *m/z* (HRMS, FAB) 418.1624 ($[M+H]^+$ $C_{20}H_{24}N_3O_7$ requires 418.1614) ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.02 (m, 1H, H2′), 2.05 (s, 3H, CH_3COO), 2.10 (s, 3H, CH_3COO), 2.43 (ddd, $J_{H2'',H3'} = 1.8$ Hz, $J_{H2'',H1'} = 5.6$ Hz, $J_{gem} = 14.3$ Hz, 1H, H2″), 4.04–4.16 (m, 3H, CH_2–7, H5″), 4.19 (m, 1H, H4′), 4.27 (dd, $J_{H5',H4'} = 4.9$ Hz, $J_{gem} = 11.2$ Hz, 1H, H5′), 5.11 (dt, $J_{H3',H2''} = J_{H3',H4'} = 1.9$ Hz, $J_{H3',H2'} = 6.4$ Hz, 1H, H3′), 6.28 (dd, $J_{H1',H2''} = 5.5$ Hz, $J_{H1',H2'} = 8.6$ Hz, 1H, H1′), 6.58–6.65 (m, 2H, Ph-o), 6.73 (m, 1H, Ph-p), 7.12–7.22 (m, 2H, Ph-m), 7.44 (t, $^4J_{H6,H7} = 1.2$ Hz, 1H, H6);

^{13}C NMR (63 MHz, $CDCl_3$) δ 20.83 (*C*H_3COO), 20.97 (*C*H_3COO), 37.48 (C2′), 41.03 (C7), 63.80 (C5′), 74.25 (C3′), 82.40 (C4′), 85.31 (C1′), 112.51 (C5), 113.52 (Ph-o), 118.36 (Ph-p), 129.42 (Ph-m), 136.19 (C6), 147.39 (Ph-i), 150.44 (C2), 163.50 (C4), 170.48 (CH_3*C*OO), 170.67 (CH_3*C*OO); UV(MeOH) $\lambda_{max} = 248$ nm ($\varepsilon = 11000$).

4f *Z* and *E* isomers; *m/z* (HRMS, FAB) 418.1629 ($[M+H]^+$ $C_{20}H_{24}N_3O_7$ requires 418.1614) ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.10 (s, 3H, CH_3COO of *Z*), 2.12 (s, 3H, CH_3COO of *Z*), 2.03–2.31 (m, 10H, 2xCH_3COO of *E*, H2′, H2″ of *Z* and *E*), 3.81 (dd, $^4J_{H6,H7} = 1.9$ Hz, $J_{gem} = 13.9$ Hz, 1H, one of CH_2 -6 of *E*), 3.92 (dd, $^4J_{H6,H7} = 0.7$ Hz, $J_{gem} = 13.1$ Hz, 1H, one of CH_2–6 of *Z*), 4.04–4.40 (m, 7H, one of CH_2–6, H4′ of *Z* and *E*, H5′, H5″ of *Z*, H5″ of *E*), 4.69 (dd, $J_{H5',H4'} = 9.5$ Hz, $J_{gem} = 12.1$ Hz, 1H, H5′ of *E*), 5.08–5.18 (m, 2H, H3′ of *Z* and *E*), 5.21 (m, 1H, PhN*H*CH of *E*), 6.34 (dd, $J = 6.1$ Hz, $J = 8.6$ Hz, 1H, H1′ of *Z*), 6.42 (dd, $J_{H1',H2''} = 5.2$ Hz, $J_{H1',H2'} = 9.6$ Hz, 1H, H1′ of *E*), 6.54–7.48 (m, 13H, Ph, N*H*-3 of *Z* and *E*, H7 of *Z*), 8.06 (dt, $^4J_{H7,H6} = 1.7$ Hz, $J_{H7,NH} = 13.8$ Hz, 1H, H7 of *E*), 10.29 (d, $J_{NH,H7} = 12.6$ Hz, 1H, PhN*H*CH of *Z*); ^{13}C NMR (63 MHz, $CDCl_3$) δ, 20.93 (*C*H_3COO of *E* and *Z*), 21.09 (*C*H_3COO of *E* and *Z*), 32.90 (C2′of *E*), 33.45 (C2′ of *Z*), 36.38 (C6 of *E*), 40.35 (C6 of *Z*), 64.10 (C5′ of *Z* and *E*), 74.38 (C3′ of *Z* and *E*), 80.70 (C4′of *Z*), 81.73 (C4′ of *E*), 84.42 (C1′ of *Z*), 85.38 (C1′ of *E*), 89.92 (C5 of *Z*), 92.50 (C5 of *E*), 115.85 (Ph-o of *E*), 115.98 (Ph-o of *Z*), 130.27 (Ph-m of *E*), 130.35 (Ph-m of *Z*), 131.68 (Ph-p of *E*), 132.01 (Ph-p of *Z*), 137.65 (C7 of *E*), 138.53 (Ph-i of *Z*), 139.41 (Ph-i of *E*), 141.02 (C7 of *Z*), 152.44 (C2 of *E*), 153.25 (C2 of *Z*), 165.03 (C4 of *E*), 166.99 (C4 of *Z*),

170.66 (CH_3COO of *Z* and *E*), 170.74, (CH_3COO of *Z* and *E*); UV(MeOH) $\lambda_{max} = 340.5$ nm ($\varepsilon = 20600$).

Undirect Reductive Amination with *p*-Toluidine

Isolated products: **3g**, 293 mg, yield 68%; **4g**, 65 mg, yield 15%.

TLC: **3g** R_f 0.24 and **4g** R_f 0.28, 0.47 in ($CHCl_3$/MeOH 95:5); **3g** R_f 0.15 and **4g** R_f 0.23, 0.46 (AcOEt/MeOH 98:2).

Spectral Data for 3g and 4g Z and E Isomers

3g: *m/z* (HRMS, FAB) 432.1784 ($[M+H]^+$ $C_{21}H_{26}N_3O_7$ requires 432.1771); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.03 (m, 1H, H2′), 2.05 (s, 3H, C*H*$_3$COO), 2.10 (s, 3H, C*H*$_3$COO), 2.22 (s, 3H, C*H*$_3$Ph), 2.43 (ddd, $J_{H2'',H3'} = 1.8$ Hz, $J_{H2'',H1'} = 5.6$ Hz, $J_{gem} = 14.2$ Hz, 1H, H2″), 4.00–4.17 (m, 3H, C*H*$_2$–7, H5″), 4.19 (m, 1H, H4′), 4.27 (dd, $J_{H5',H4'} = 4.6$ Hz, $J_{gem} = 11.2$ Hz, 1H, H5′), 5.11 (dt, $J_{H3',H2''} = J_{H3',H4'} = 1.6$ Hz, $J_{H3',H2'} = 6.3$ Hz, 1H, H3′), 6.27 (dd, $J_{H1',H2''} = 5.6$ Hz, $J_{H1',H2'} = 8.6$ Hz, 1H, H1′), 6.44–6.64 (m, 2H, Ph-o), 6.83–7.07 (m, 2H, Ph-m), 7.43 (t, $^4J_{H6,H7} = 1.1$ Hz, 1H, H6); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.43 (*C*H$_3$COO), 20.79 (*C*H$_3$COO), 20.94 (*C*H$_3$Ph), 37.45 (C2′), 41.46 (C7), 63.79 (C5′), 74.26 (C3′), 82.35 (C4′), 85.26 (C1′), 112.64 (C5), 113.80 (Ph-o), 127.65 (Ph-p), 129.88 (Ph-m), 136.18 (C6), 145.00 (Ph-i), 150.45 (C2), 163.48 (C4), 170.46 (CH_3COO), 170.48 (CH_3COO); UV(MeOH) $\lambda_{max} = 247$ nm ($\varepsilon = 12300$).

4g *Z* and *E* isomers; *m/z* (HRMS, FAB) 432.1765 ($[M+H]^+$ $C_{21}H_{26}N_3O_7$ requires 432.1771); ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.11 (s, 3H, C*H*$_3$COO of *Z*), 2.12 (s, 3H, C*H*$_3$COO of *Z*), 2.06–2.41 (m, 13H, 2xC*H*$_3$COO, C*H*$_3$Ph of *E*, H2′, H2" of *Z* and *E*), 2.31 (s, 3H, C*H*$_3$Ph of *Z*), 3.81 (dd, $^4J_{H6,H7} = 1.8$ Hz, $J_{gem} = 13.9$ Hz, 1H, one of C*H*$_2$ -6 of *E*), 3.92 (d, $J_{gem} = 13.6$ Hz, 1H, one of C*H*$_2$–6 of *Z*), 4.04–4.18 (m, 3H, one of C*H*$_2$–6 of *Z* and *E*, H4′ of *Z*), 4.19–4.41 (m, 4H, H5′, H5″ of *Z*, H4′, H5″ of *E*), 4.70 (dd, $J_{H5',H4'} = 9.4$ Hz, $J_{gem} = 12.1$ Hz, 1H, H5′ of *E*), 5.09–5.17 (m, 2H, H3′ of *Z* and *E*), 5.21 (m, 1H, PhN*H*CH of *E*), 6.34 (dd, $J_{H1',H2''} = 6.1$ Hz, $J_{H1',H2'} = 8.7$ Hz, 1H, H1′ of *Z*), 6.41 (dd, $J_{H1',H2''} = 5.0$ Hz, $J_{H1',H2'} = 9.3$ Hz, 1H, H1′ of *E*), 6.86–7.47 (m, 10H, Ph, N*H*-3 of *Z* and *E*), 7.31 (d, $J_{H7,NH} = 12.7$ Hz, 1H, H7 of *Z*), 8.03 (m, 1H, H7 of *E*), 10.24 (d, $J_{NH,H7} = 12.6$ Hz, 1H, PhN*H*CH of *Z*); ^{13}C NMR (63 MHz, $CDCl_3$) δ, 20.81 (*C*H$_3$Ph), 21.07 (2x*C*H$_3$COO of *E* and *Z*), 32.85 (C2′of *E*), 33.43 (C2′ of *Z*), 36.44 (C6 of *E*), 40.40 (C6 of *Z*), 64.11(C5′ of *Z* and *E*), 74.34 (C3′ of *Z*), 74.45(C3′ of *E*), 80.62 (C4′of *Z*), 81.60 (C4′ of *E*), 84.33 (C1′ of *Z*), 85.35 (C1′ of *E*), 89.86 (C5 of *Z*), 92.47 (C5 of *E*), 115.89 (Ph-o of *E*), 116.05 (Ph-o of *Z*), 130.31 (Ph-m of *E*), 130.39 (Ph-m of *Z*), 132.89 (Ph-p of *E*), 133.22 (Ph-p of *Z*), 137.81 (C7 of *E*), 137.96 (Ph-i of *Z*), 138.52 (Ph-i of *E*), 141.22 (C7 of *Z*), 152.47 (C2 of *E*), 153.27 (C2 of *Z*), 164.99 (C4 of *E*), 166.96 (C4 of *Z*), 170.68 (CH_3COO

of *Z* and *E*), 170.76, (CH_3COO of *Z* and *E*); UV(MeOH) $\lambda_{max} = 340$ nm ($\varepsilon = 21000$).

Undirect Reductive Amination with *p*-Nitroaniline

Isolated products: **3h**, 254 mg, yield 55%; **4h**, 28 mg, yield 6%

TLC : **3h** R_f 0.23 and **4h** R_f 0.43, 0.53 in ($CHCl_3$/MeOH 95:5); **3h** R_f 0.10 and **4h** R_f 0.23, 0.44 (AcOEt/MeOH 98:2).

Spectral Data for 3h and 4h Z and E Isomers

3h: *m/z* (HRMS, FAB) 463.1452 ($[M+H]^+$ $C_{20}H_{23}N_4O_9$ requires 463.1465 ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.04 (m, 1H, H2′), 2.10 (s, 3H, C*H*$_3$COO), 2.12 (s, 3H, C*H*$_3$COO), 2.53 (ddd, $J_{H2'',H3'} = 1.8$ Hz, $J_{H2'',H1'} = 5.5$ Hz, $J_{gem} = 14.3$ Hz, 1H, H2″), 4.16–4.52 (m, 5H, C*H*$_2$–7, H4′, H5′, H5″), 5.13 (dt, $J_{H3',H2''} = J_{H3',H4'} = 2.0$ Hz, $J_{H3',H2'} = 6.6$ Hz, 1H, H3′), 6.24 (dd, $J_{H1',H2''} = 5.4$ Hz, $J_{H1',H2'} = 8.4$ Hz, 1H, H1′), 6.60–6.74 (m, 2H, Ph-o), 7.59 (s, 1H, H6), 8.03–8.14 (m, 2H, Ph-m); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.97 (2x*C*H$_3$COO), 37.69 (C2′), 40.16 (C7), 63.78 (C5′), 74.07 (C3′), 82.78 (C4′), 85.90 (C1′), 111.12 (C5), 111.60 (Ph-o), 126.42 (Ph-m), 137.18 (C6), 138.29 (Ph-i), 150.22 (C-2), 153.06 (Ph-p), 163.58 (C4), 170.53 (CH_3COO), 170.85 (CH_3COO); UV(MeOH) $\lambda_{max} = 260$ nm ($\varepsilon = 8200$), $\lambda_{max} = 380$ nm ($\varepsilon = 16500$).

4h *Z* and *E* isomers; *m/z* (HRMS, FAB) 463.1447 ($[M+H]^+$ $C_{20}H_{23}N_4O_9$ requires 463.1465) ^{1}H NMR (250 MHz, CDCl3) δ 2.12 (s, 3H, C*H*$_3$COO of *Z*), 2.13 (s, 3H, C*H*$_3$COO of *Z*), 2.09–2.23 (m, 10H, 2xC*H*$_3$COO of *E*, H2′, H2″ of *Z* and *E*), 3.86 (dd, $^4J_{H6,H7} = 1.9$ Hz, $J_{gem} = 14.6$ Hz, 1H, one of C*H*$_2$ -6 of *E*), 3.98 (dd, $^4J_{H6,H7} = 0.9$ Hz, $J_{gem} = 13.5$ Hz, 1H, one of C*H*$_2$–6 of *Z*), 4.12–4.46 (m, 7H, one of C*H*$_2$–6, H4′ of *Z* and *E,* H5′, H5″ of *Z*, H5″ of *E*), 4.75 (dd, $J_{H5',H4'} = 9.9$ Hz, $J_{gem} = 12.1$ Hz, 1H, H5′ of *E*), 5.07–5.16 (m, 1H, H3′ of *Z* and *E*), 5.24 (m, 1H, PhN*H*CH of *E*), 6.35 (dd, $J_{H1',H2''} = 6.6$ Hz, $J_{H1',H2'} = 8.1$ Hz, 1H, H1′ of *Z*), 6.40 (m, 1H, H1′ of *E*), 7.05–7.16 (m, 2H, Ph-o of *Z*), 7.21–7.27 (m, 2H, Ph-o of *E*), 7.44 (d, $J = 12.1$ Hz, 1H,H7 of *Z*), 7.56 (s, 1H, N*H*-3 of *E*), 7.74 (s, 1H, N*H*-3 of *Z*), 8.18–8.29 (m, 5H, Ph-m of *Z* and *E*, H7 of *E*), 10.56 (d, $J_{NH,H7} = 12.0$ Hz, 1H, PhN*H*CH of *Z*); ^{13}C NMR (63 MHz, $CDCl_3$) δ 20.99 (*C*H$_3$COO of *E* and *Z*), 21.10 (*C*H$_3$COO of *E* and *Z*), 33.04 (C2′of *E*), 33.55 (C2′ of *Z*), 36.26 (C6 of *E*), 40.29 (C6 of *Z*), 64.03 (C5′ of *Z* and *E*), 74.26 (C3′ of *Z* and *E*), 80.96 (C4′of *Z*), 81.96 (C4′ of *E*), 84.51 (C1′ of *Z*), 85.54 (C1′ of *E*), 95.06 (C5 of *Z*), 98.99 (C5 of *E*), 115.01(Ph-o of *Z* and *E*), 126.25 (Ph-m of *Z* and *E*), 135.25 (C7 of *E*), 138.45 (C7 of *Z*), 142.75 (Ph-i of *E*), 142.85 (Ph-i of *E*), 145.58 (Ph-p of *E*), 145.71 (Ph-p of *Z*), 151.40 (C2 of *E*), 152.67 (C2 of *Z*), 164.55 (C4 of *E*), 166.94 (C4 of *Z*), 170.64 (CH_3COO of *Z* and *E*), 170.72, (CH_3COO of *Z* and *E*); UV(MeOH) $\lambda_{max} = 372.5$ nm ($\varepsilon = 21500$).

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