

Full Paper

## A Convenient Asymmetric Synthesis of a $\beta$ -amino Ester with Additional Functionalization as a Precursor for Peptide Nucleic Acid (PNA) Monomers

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**Abstract:** We report the asymmetric synthesis of di-3-pentyl (3*S*, $\alpha$ *S*,7*E*)-3-*N*-benzyl-*N*- $\alpha$ -methylbenzylamino-dec-7-enedioate (**9**), which contains the correct functionalization to produce  $\delta$ -amino acid derivatives to be used as monomers for Peptide Nucleic Acid (PNA) formation. With this aim, thymine-pentanoic acid **15** and some of its ester derivatives were obtained, their reactivity was studied and the noteworthy ethyl ester **12** was quantitatively produced by transesterification of methyl ester **11**, thus paving the way for the synthesis of the thymine-containing amino ester **IV**, which has been designed as a building block for a Nucleic-Acid analog with a chiral, flexible peptide backbone.

**Keywords:** Peptide nucleic acids (PNA), thymine derivatives, transesterification, asymmetric synthesis,  $\beta$ -amino acids.

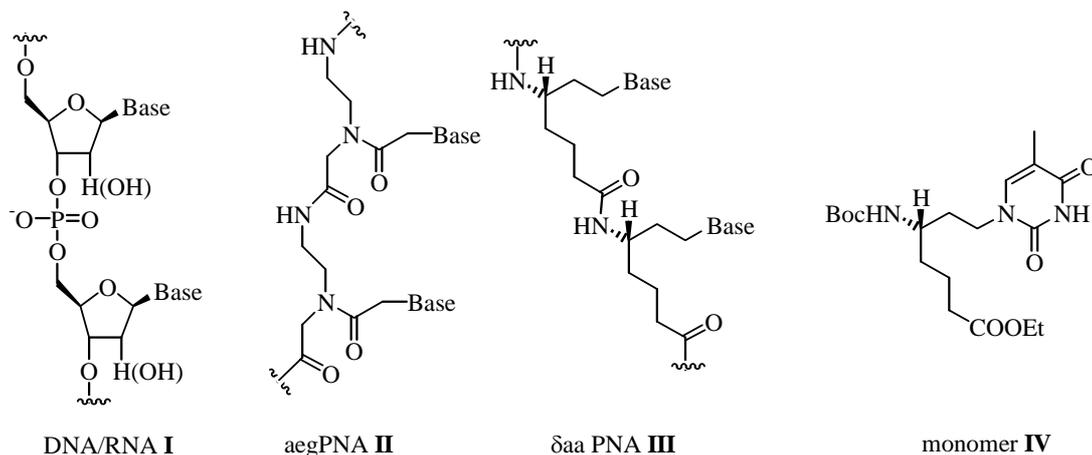
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### Introduction

Recently, the chemistry of nucleic-acid analogs (Figure 1, DNA/RNA **I**) has gained considerable attention due to their potential use as antisense or antigene agents [1]. Among the known oligonucleotide analogues [2,3], acyclic *N*-(2-aminoethyl)-glycyl peptide nucleic acids (Figure 1, aegPNA **II**), are found to be very good mimics of DNA/RNA hybrids, and their stability towards proteases and nucleases has generated interest in medicinal chemistry [3]. A great deal of work is

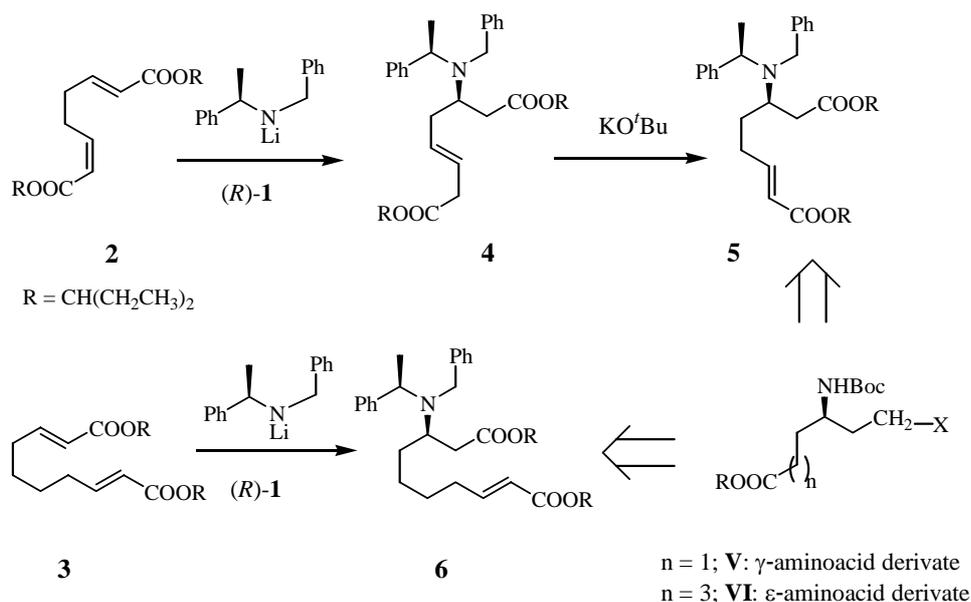
currently being undertaken in this field [4]. Leumann *et al.* [5] decided to investigate the influence of higher flexibility of the amide backbone (relative to PNA) of the base-pairing properties with complementary DNA and RNA (Figure 1,  $\delta$ aa PNA **III**). They performed the synthesis of the monomer building block **IV** (Figure 1), related to the repeating monomeric  $\delta$ -amino acid in **III**, containing the nucleobase thymine.

**Figure 1.** Structure of DNA, PNA and modified PNAs.



We have demonstrated the asymmetric synthesis of the monoaddition products **5** and **6** by chiral lithium amide [(*R*)-**1**] Michael addition to diendioate esters **2** and **3** respectively (Scheme 1) [6]. While addition to (*E,E*)-octa-2,6-diendioate gave the cyclopentane adduct through a domino reaction initiated by an asymmetric Michael addition, followed by a 5-*exo-trig* intramolecular cyclization [7], addition to the (*E,Z*)-counterpart gave the monoaddition adduct **4**, as it is known that lithium amide does not produce addition to (*Z*)- $\alpha,\beta$ -unsaturated esters [8].

**Scheme 1.**

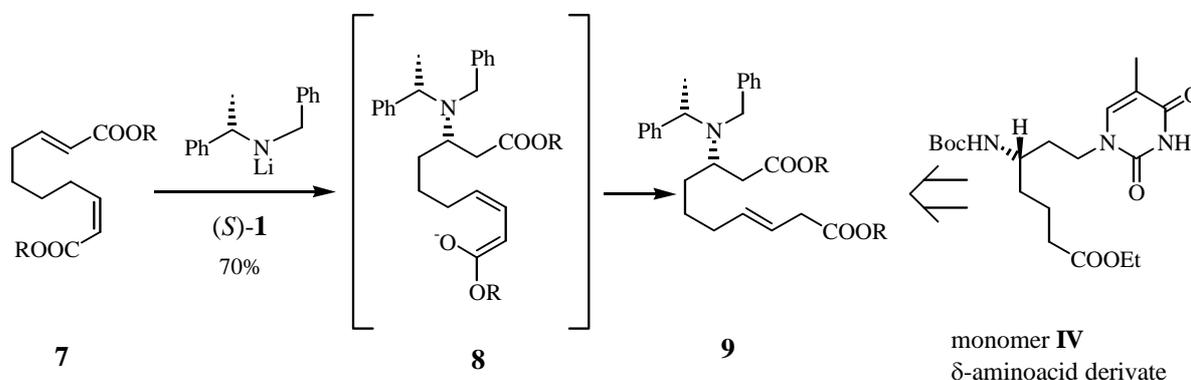


The monoaddition product **6** is obtained instead by treating the acceptor **3** with an equimolecular amount of the lithium amide, as an excess of amide produces the diaddition adduct [6]. We envisaged that degradation of the remaining alkenes in these compounds and subsequent transformation of the ester group would make them precursors of  $\gamma$ - and  $\epsilon$ -amino acid derivatives, **V** and **VI** respectively. Davies *et al.* [9] has recently published a comprehensive review in this area of chemistry covering the scope, limitation and synthetic applications of the use of enantiomerically pure lithium amides as homochiral ammonia equivalents in conjugate addition reactions. We present here the synthesis of monoaddition adduct **9** precursor of **IV**, and the study of the reactivity of thymine-pentanoic acid and derivatives, with similar functionality, in order to apply the results to the synthesis of PNA monomers.

## Results and Discussion

Whereas (*E*)- $\alpha,\beta$ -unsaturated esters are very susceptible to conjugate addition, their (*Z*)-counterparts are highly susceptible to  $\gamma$ -deprotonation [8,9]. This suggested a strategy towards the monoadduct **9** from di-3-pentyl (*E,Z*)-deca-2,8-diendioate **7**. Addition of **7** to an excess (3 equiv.) of (*S*)-**1** generated the (*E*)- $\beta,\gamma$ -unsaturated monoadduct **9**,  $[\alpha]_D^{26} = -6.9$  (c 0.93,  $\text{CHCl}_3$ ), in 70% yield after work-up and > 95% de [6], as expected from  $\alpha$ -protonation of the intermediate dienoate **8** (Scheme 2). The absolute configuration at C(3) within (*3S,\alpha S*)-**9** relative to the N- $\alpha$ -methylbenzyl stereocentre is assigned by analogy with previous authenticated models developed to explain the stereoselectivity observed during addition of lithium amide (*S*)-**1** to  $\alpha,\beta$ -unsaturated acceptors [10].

Scheme 2.



We propose the monoadduct **9** as a precursor of the the  $\delta$ -aminoacid monomer **IV**, via transformation of the ester group and degradation of the remaining double bond in **9** to an ester, further work within our group haven proven that the double bond can easily be transformed into an aldehyde, the corresponding dioxolane derivative or the related methyl ester [11]. We envisaged performing some reactions once the thymine nucleobase is attached, so we decided to synthesize the methyl thymine-pentanoate **11** and undertake the reactions shown in Scheme 3. It is of great interest to achieve, with the nucleobase attached, the transesterification process from methyl or other alkyl ester to the ethyl one, which is the ester group in the compound **IV** described in the literature [5], in order to ascertain the optical rotation and thereby the enantiomeric excess produced over the whole process. Nevertheless, the reactions shown in scheme 3, and the preparation of thymine pentanoic acid **15** are



## Conclusions

We have demonstrated an efficient strategy for the asymmetric synthesis of  $\beta$ -amino ester **9** by asymmetric Michael addition of (*S*)-**1** to the (*E*) double bond and  $\gamma$ -deprotonation of the (*Z*) double bond in the (*E,Z*)-deca-2,8-diendioate ester **7**. Reactivity assays on the nucleobase containing the model thymine-pentanoic acid and derivatives showed that they are prone to degradation upon treatment with oxidants such as O<sub>3</sub> or NaClO<sub>2</sub>; the oxidation of dioxolane **14** to produce ester **17**, needs further study. On the other hand, the aldehyde and acid functions in **13** and **11** can be easily interchanged; the diazomethane esterification of the acid function in compound **15** is competitive with nitrogen methylation of the thymine moiety, but interestingly, quantitative transesterification of methyl ester **11** to produce ethyl ester **12** was achieved, paving the way to obtain the required ester in the preparation of the previously synthesized  $\delta$ -amino acid **IV**. The application of this strategy for the preparation of  $\delta$ -amino acid monomer **IV** is currently under investigation in our laboratory and will be published in due course.

## Experimental Section

### General

<sup>1</sup>H-NMR and <sup>13</sup>C-NMR spectra were recorded in CDCl<sub>3</sub> at 200 and 400 MHz (<sup>1</sup>H) or 50 and 100 MHz (<sup>13</sup>C) on Varian 200 VX and Bruker DRX 400 instruments, respectively. Multiplicities were determined by DEPT experiments. IR spectra were recorded using a BOMEM 100 FTIR spectrophotometer. Optical rotations were determined using a Perkin-Elmer 241 polarimeter in a 1 dm cell and are given in units of 10<sup>-1</sup> deg cm<sup>2</sup> g<sup>-1</sup>. Concentrations are quoted in g per 100mL. The electron impact (EI) mass spectra were run on a VG-TS 250 spectrometer using a 70 eV ionizing voltage. HRMS were recorded using a VG Platform (Fisons) spectrometer using Chemical Ionization (ammonia as gas) or Fast Atom Bombardment (FAB) techniques. Thin layer chromatography (tlc) was performed on aluminum sheets coated with 60 F254 silica. Sheets were visualized using iodine, UV light or 1% aqueous KMnO<sub>4</sub> solution. Column chromatography (CC) was performed with Merck silica gel 60 (70- 230 mesh). Solvents and reagents were generally distilled prior to use: DMF from CaH<sub>2</sub> and dichloromethane (DCM) from KOH.

### Preparation of di-3-pentyl (3*S*, $\alpha$ *S*,7*E*)-2-*N*-benzyl-*N*- $\alpha$ -methylbenzylamino-dec-7-enedioate (**9**)

*n*-BuLi (1.6 M, 0.41 mL, 0.66 mmol) was added to a stirred solution of (*S*)-*N*-benzyl-*N*- $\alpha$ -methylbenzylamine (145 mg, 0.69 mmol) in THF (3 mL) at  $-78^{\circ}\text{C}$  and the mixture stirred for 30 minutes prior to the addition of a solution of **7** (76 mg, 0.22 mmol) in THF (1 mL) at  $-78^{\circ}\text{C}$ . After 80 minutes, saturated aqueous NH<sub>4</sub>Cl solution was added and the resulting solution warmed to r.t., partitioned between DCM (3 x 50 mL) and brine and dried over Na<sub>2</sub>SO<sub>4</sub>. Concentration followed by flash chromatography on silica gel (95:5 Hex-EtOAc) gave **9** (85 mg, 70%); IR (film)  $\nu$  (cm<sup>-1</sup>): 2971, 2880, 1732, 1458, 1260, 1157, 1117, 968; <sup>1</sup>H-NMR (400 MHz): 0.84 (6H, t, *J* = 7.5 Hz, CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 0.89 (6H, t, *J* = 7.5 Hz, CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 1.34 (3H, d, *J* = 7.0 Hz, C( $\alpha$ )*Me*), 1.50 (4H, m, *H*-4 and *H*-5), 1.57 (8H, m, CH(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>), 1.98 (4H, m, *H*-2 and *H*-6), 3.01 (2H, d, *J* = 5.1 Hz, *H*-9), 3.36 (1H, m, *H*-3),

3.49 (1H, d,  $J = 13.9$  Hz,  $NCH_AHPh$ ), 3.81 (1H, d,  $J = 13.9$  Hz,  $NCHH_BPh$ ), 3.82 (1H, q,  $J = 7.0$  Hz,  $C(\alpha)H$ ), 4.68 (1H, quin,  $J = 5.4$  Hz,  $CH(CH_2CH_3)_2$ ), 4.77 (1H, quin,  $J = 5.4$  Hz,  $CH(CH_2CH_3)_2$ ), 5.54 (2H, m,  $H-7$  and  $H-8$ ), 7.21-7.41 (10 H, m, Ar- $H$ );  $^{13}C$ -NMR (50 MHz): 9.5 (4  $CH_3$ ,  $CH(CH_2CH_3)_2$ ), 20.5 ( $CH_3$ ,  $C(\alpha)Me$ ), 26.3 (2 $CH_2$ ,  $CH(CH_2CH_3)_2$ ), 26.5 (2 $CH_2$ ,  $CH(CH_2CH_3)_2$ ), 26.6 ( $CH_2$ ,  $C-5$ ), 32.4 ( $CH_2$ ,  $C-4$ ), 33.2 ( $CH_2$ ,  $C-6$ ), 36.7 ( $CH_2$ ,  $C-2$ ), 38.5 ( $CH_2$ ,  $C-9$ ), 50.1 ( $CH_2$ ,  $NCH_2Ph$ ), 53.7 ( $CH$ ,  $C-3$ ), 58.3 ( $CH$ ,  $C(\alpha)H$ ), 76.6 ( $CH$ ,  $CH(CH_2CH_3)_2$ ), 77.0 ( $CH$ ,  $CH(CH_2CH_3)_2$ ), 122.0 ( $CH$ ,  $C-7$ ), 134.4 ( $CH$ ,  $C-8$ ), 126.6-128.2 (10 $CH$ , Ar- $C$ ), 141.8 (C,  $C_{ipso}$ ), 142.9 (C,  $C_{ipso}$ ), 172.6 (2C, COOR); EIMS  $m/z$  (%): 549 ( $M^+$ , 10), 462 (8), 352 (40), 248 (15); HRMS (EI):  $C_{35}H_{51}NO_4$ ,  $M^+$  requires 549.382; found 549.383;  $[\alpha]_D^{26} = -6.9$  ( $c = 0.93$ ,  $CHCl_3$ ).

#### Preparation of 1-(4'-methoxycarbonylbutyl)-thymine (11)

5-Bromovaleric acid **10** (300 mg, 1.6 mmol) was treated with a solution of gaseous  $CH_2N_2$  in ether and stirred for 3 hours. Evaporation of the solvent gave methyl-5-bromo-pentanoate (300 mg, 96%); IR (film)  $\nu$  ( $cm^{-1}$ ): 2953, 1740, 1437, 1364, 1260, 1206, 1173, 1125, 1035;  $^1H$ -NMR (200 MHz): 1.60-1.95 (4H, m,  $H-3$  and  $H-4$ ), 2.27 (2H, m,  $H-2$ ), 3.33 (2H, m,  $H-5$ ), 3.59 (3H, s, COOMe);  $^{13}C$ -NMR (50 MHz): 23.6 ( $CH_2$ ,  $C-3$ ), 32.1 ( $CH_2$ ,  $C-2$ ), 32.2 (2 $CH_2$ ,  $C-4$  and  $C-5$ ), 51.7 ( $CH_3$ , COOMe), 173.6 (C, COOMe); EIMS  $m/z$  (%): 196 ( $M^+$ ), 167 (15), 165 (15), 137 (12), 115 (100), 101 (45), 89 (40). To a solution of thymine (479 mg, 4.6 mmol) in DMF (400 mL),  $K_2CO_3$  (317 mg) and  $Bu_4NI$  (124 mg) were added and the reaction mixture was stirred for 30 minutes at  $0^\circ C$  and at  $65^\circ C$  for another 30 minutes. To this solution the previously synthesized methyl-5-bromopentanoate (1.53 mmol) was added and the mixture was stirred at  $65^\circ C$  overnight. The reaction mixture was then cooled to r.t. and extracted with EtOAc. The organic layer were washed with water and dried over  $Na_2SO_4$ . Concentration followed by flash chromatography on silica gel (95:5 DCM-MeOH) gave **11** (228 mg, 62%); IR (film)  $\nu$  ( $cm^{-1}$ ): 3190, 3057, 2955, 1720, 1684, 1458, 1362, 1204, 1082;  $^1H$ -NMR (200 MHz): 1.61-1.80 (4H, m,  $H-2'$  and  $H-3'$ ), 1.91 (3H, s, Me), 2.36 (2H, t,  $J = 8.0$  Hz,  $H-4'$ ), 3.67 (3H, s, COOMe), 3.70 (2H, t,  $J = 8.0$  Hz,  $H-1'$ ), 6.98 (1H, s,  $H-6$ ), 9.10 (1H, m, NH);  $^{13}C$ -NMR (50 MHz): 12.1 ( $CH_3$ , Me), 21.5 ( $CH_2$ ,  $C-3'$ ), 28.3 ( $CH_2$ ,  $C-2'$ ), 33.2 ( $CH_2$ ,  $C-4'$ ), 47.8 ( $CH_2$ ,  $C-1'$ ), 51.4 ( $CH_3$ , COOCH $_3$ ), 110.4 (C,  $C-5$ ), 140.6 (CH,  $C-6$ ), 151.2 (C,  $C-2$ ), 164.8 (C,  $C-4$ ), 173.4 (C, COOCH $_3$ ); EIMS  $m/z$  (%): 240 ( $M^+$ , 52), 209 (42), 180 (25), 140 (39), 126 (62), 110 (38), 96 (100); HRMS (EI):  $C_{11}H_{16}O_4N_2$  requires 240.111; found 240.113.

#### Preparation of 1-(4'-ethoxycarbonylbutyl)-thymine (12)

A solution of **11** (17 mg, 0.07 mmol) in EtOH (5 mL) at  $0^\circ C$  was treated with a stream of gaseous HCl till the mixture was saturated. The solution was stirred overnight at r.t., and the solvent was then removed under vacuum to give **12** (19 mg, 99%); IR (film)  $\nu$  ( $cm^{-1}$ ): 3185, 3057, 2955, 1724, 1684;  $^1H$ -NMR (200 MHz): 1.24 (3H, t,  $J = 6.8$  Hz,  $CO_2CH_2CH_3$ ), 1.60-1.80 (4H, m,  $H-3'$  and  $H-2'$ ), 1.91 (3H, s, Me), 2.35 (2H, m,  $H-4'$ ), 3.70 (2H, m,  $H-1'$ ), 4.12 (2H, q,  $J = 6.8$  Hz,  $CO_2CH_2CH_3$ ), 6.98 (1H, s,  $H-6$ ), 9.22 (1H, s, NH);  $^{13}C$ -NMR (50 MHz): 12.3 ( $CH_3$ , Me), 14.2 ( $CH_3$ ,  $CO_2CH_2CH_3$ ), 21.7 ( $CH_2$ ,  $C-3'$ ), 28.4 ( $CH_2$ ,  $C-2'$ ), 33.2 ( $CH_2$ ,  $C-4'$ ), 48.2 ( $CH_2$ ,  $C-1'$ ), 60.2 ( $CH_2$ ,  $CO_2CH_2CH_3$ ), 110.7 (C,  $C-5$ ),

140.4 (CH, C-6), 150.8 (C, C-2), 164.3 (C, C-4), 173.0 (C, CO<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>); HRMS (EI): C<sub>12</sub>H<sub>18</sub>O<sub>4</sub>N<sub>2</sub> requires 254.127; found 254.127.

#### Preparation of 1-(5'-oxopentyl)-thymine (**13**)

To a solution of **11** (99 mg, 0.41 mmol) in DCM (4 mL) at -78°C, DIBAL-H (0.9 mL, 1.0 M) was added. The reaction mixture was stirred for 1 hour at -40°C and then H<sub>2</sub>O was added. The resulting solution was warmed to r.t and added to a mixture of NaHCO<sub>3</sub> and Na<sub>2</sub>SO<sub>4</sub> in ether. It was then filtered through Celite<sup>®</sup> and concentrated *in vacuo* to give **13** (60 mg, 69%); IR (film)  $\nu$  (cm<sup>-1</sup>): 3187, 3048, 2947, 1684, 1472, 1362, 1258, 1221, 1094; <sup>1</sup>H-NMR (200 MHz): 1.62-1.81 (4H, m, H-2' and H-3'), 1.90 (3H, s, Me), 2.52 (2H, t, *J* = 8.0 Hz, H-4'), 3.70 (2H, t, *J* = 8.0 Hz, H-1'), 6.98 (1H, s, H-6), 9.35 (1H, s, NH), 9.77 (1H, s, CHO).

#### Preparation of 1-(4'-[1,3]dioxolan-2-yl-butyl)-thymine (**14**)

*p*-TsOH and ethane-1,2-diol were added to a solution of **13** (69 mg, 0.33 mmol) in dry benzene. The reaction mixture was refluxed in a Dean Stark apparatus for 12 hours. The solution was cooled and then H<sub>2</sub>O (1 mL) was added, extracted with Et<sub>2</sub>O and the organic layer washed with NaHCO<sub>3</sub> and brine, dried and concentrated *in vacuo* to give **14** (60 mg, 72%); IR (film)  $\nu$  (cm<sup>-1</sup>): 3196, 3059, 2953, 1688, 1472, 1362, 1221, 1177, 1130; <sup>1</sup>H-NMR (200 MHz): 1.62-1.85 (4H, m, H-2', H-3' and H-4'), 1.91 (3H, s, Me), 3.69 (2H, t, *J* = 8.0 Hz, H-1'), 3.83 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 3.95 (2H, m, OCH<sub>2</sub>CH<sub>2</sub>O), 4.85 (1H, t, *J* = 8.0 Hz, H-5'), 6.97 (1H, s, H-6), 8.82 (1H, s, NH); <sup>13</sup>C-NMR (50 MHz): 12.5 (CH<sub>3</sub>, Me), 21.0 (CH<sub>2</sub>, C-3'), 29.1 (CH<sub>2</sub>, C-2'), 33.7 (CH<sub>2</sub>, C-4'), 48.6 (CH<sub>2</sub>, C-1'), 65.0 (CH<sub>2</sub>, OCH<sub>2</sub>CH<sub>2</sub>O), 65.1 (CH<sub>2</sub>, OCH<sub>2</sub>CH<sub>2</sub>O), 104.3 (CH, C-5'), 110.8 (C, C-5), 140.7 (CH, C-6), 150.9 (C, C-2), 164.4 (C, C-4); EIMS *m/z* (%): 254 (M<sup>+</sup>, 5), 182 (12), 153 (10), 126 (14), 96 (19), 73 (100); HRMS (EI): C<sub>12</sub>H<sub>18</sub>O<sub>4</sub>N<sub>2</sub> requires 254.1266; found 254.1298.

#### Preparation of 1-(4'-methoxycarbonyl-butyl)-3-methylthymine (**11**)

To a solution of **13** (50 mg, 0.21 mmol) in DMF (1 mL) and MeOH (0.05 mL) was added PDC (474 mg, 126 mmol) at r.t. and the mixture was stirred for 20 hours, then H<sub>2</sub>O (1 mL) was added and the reaction mixture was extracted with Et<sub>2</sub>O. The organic layer was washed with H<sub>2</sub>O and brine. It was then dried over Na<sub>2</sub>SO<sub>4</sub> and filtered. Evaporation of the solvent followed by flash chromatography on silica gel (95:5 DCM-MeOH) gave **11** (36 mg, 73%).

#### Preparation of 1-(4'-carboxybutyl)-thymine (**15**)

Compound **11** (30 mg, 0.12 mmol) was added to the solution of KOH (0.1 mL) and MeOH (2M) and was stirred at r.t. for 8 hours, then H<sub>2</sub>O was added to the reaction mixture and the solution was treated with 2M HCl to pH = 2 and extracted with Et<sub>2</sub>O. The organic extracts were washed with water to give, after drying and concentration, compound **15** (28 mg, 99%); IR (film)  $\nu$  (cm<sup>-1</sup>): 3600, 3185, 3057, 2928, 1684, 1474, 1418, 1362, 1260; <sup>1</sup>H-NMR (200 MHz): 1.61-1.82 (4H, m, H-3' and H-4'),

1.90 (3H, s, *Me*), 2.40 (2H, t,  $J = 6.8$  Hz, *H-2'*), 3.72 (2H, t,  $J = 6.8$  Hz, *H-1'*), 7.04 (1H, s, *H-6*);  $^{13}\text{C}$ -NMR (50 MHz): 14.6 ( $\text{CH}_3$ , *Me*), 25.4 ( $\text{CH}_2$ , *C-3'*), 30.8 ( $\text{CH}_2$ , *C-2'*), 31.9 ( $\text{CH}_2$ , *C-4'*), 49 ( $\text{CH}_2$ , *C-1'*), 113.8 (C, *C-5*), 145.6 (CH, *C-6*), 150.9 (C, *C-2*), 169.4 (C, *C-4*), 179.5 (C, COOH); EIMS  $m/z$  (%): 244 ( $(\text{M}+\text{NH}_4)^+$ , 38), 226 ( $\text{M}^+$ , 8), 209 (35), 126 (70), 110 (40), 96 (100). Compound **15** (10 mg, 0.05 mmol) was dissolved in a solution of gaseous  $\text{CH}_2\text{N}_2$  in ether and stirred for 30 minutes at r.t. Concentration followed by flash chromatography on silica gel (95:5 DCM-MeOH) gave **16** (5 mg, 40%) and **11** (4 mg, 40%); Compound **16**:  $^1\text{H}$ -NMR (200 MHz): 1.67-1.69 (4H, m, *H-3'* and *H-4'*), 1.93 (3H, s, *Me*), 2.36 (2H, t,  $J = 8.0$  Hz, *H-2'*), 3.34 (3H, s, *Me-N*), 3.65 (3H, s, COOMe), 3.70 (2H, t,  $J = 8.0$  Hz, *H-1'*), 7.16 (1H, s, *H-6*).

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*Sample Availability:* Contact the authors.