27. Synthesis of a Building Block for a Nucleic-Acid Analog with a Chiral, Flexible Peptide Backbone

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We present here a nine-step synthesis of the thymine-containing amino ester **1**, starting from commercially available methyl *N*-[(*tert*-butoxy)carbonyl]-L-serinate. Amino ester **1** is considered as a building block for the preparation of a new nucleic-acid analog with a chiral, flexible polyamide backbone. Key steps in the synthesis are the vitamin-B_{12}-catalyzed addition of 3-bromo-*N*-[(*tert*-butoxy)carbonyl]-L-alaninate **2** to ethyl acrylate and the homologation of the corresponding *N*-protected α-amino acid **4** into the β-amino ester **6** by *Arndt-Eistert* chemistry. The latter was found to proceed with 10% inversion of configuration at the asymmetric center in **6**. Resolution to enantiomerically pure material, however, was easily achieved by simple crystallization of **1**.

Introduction. – Recently, the chemistry of nucleic-acid analogs has gained considerable attention due to their potential use as antisense or antigene agents [1]. Within this area, a steadily growing group of analogs in which the sugar-phosphate backbone is replaced by a polyamide backbone is emerging, mainly as a consequence of the intriguing base-pairing properties of their prototype PNA (*Scheme 1*; for a recent review on the properties of PNA, see [2]). PNA itself is achiral, and only a few polyamide analogs thereof with chiral backbone are known [3–7] so far.

We decided to investigate the influence of higher flexibility of the amide backbone (relative to PNA) on the base-pairing properties with complementary DNA and RNA on the basis of the model oligomer **A**. Here, we present the synthesis of the monomer building block **1** (*Scheme 1*), related to the repeating monomeric δ-amino acid in **A**, containing the nucleobase thymine. Key steps in the synthesis are the vitamin-B_{12}-catalyzed, light-assisted radical addition of bromide **2** (derived from L-serine) with ethyl acrylate to the mixed L-α-aminoadipic diester **3**, followed by a C_1-homologation at the α-aminoester moiety *via* the *Arndt-Eistert* reaction.

Results and Discussion. – Earlier studies from our laboratory demonstrated that vitamin-B_{12}-catalyzed addition of alkyl halides to activated olefins is a useful alternative for C–C bond formation *via* radical intermediates [8–10]. We decided to further expand this chemistry with the synthesis of the key intermediate **3** having two chemically distinguishable ester functions (for a similar preparation of an L-α-adipic monoester using Bu_3SnH, see [11]).

The requisite radical precursor methyl 3-bromo-*N*-[(*tert*-butoxy)carbonyl]-L-alaninate (**2**) was prepared from the commercially available methyl *N*-[(*tert*-butoxy)carbo-

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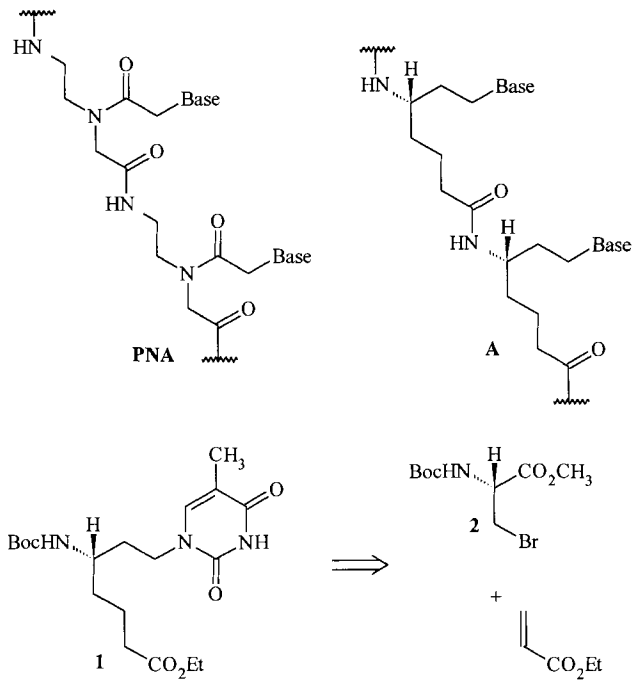
Scheme 1

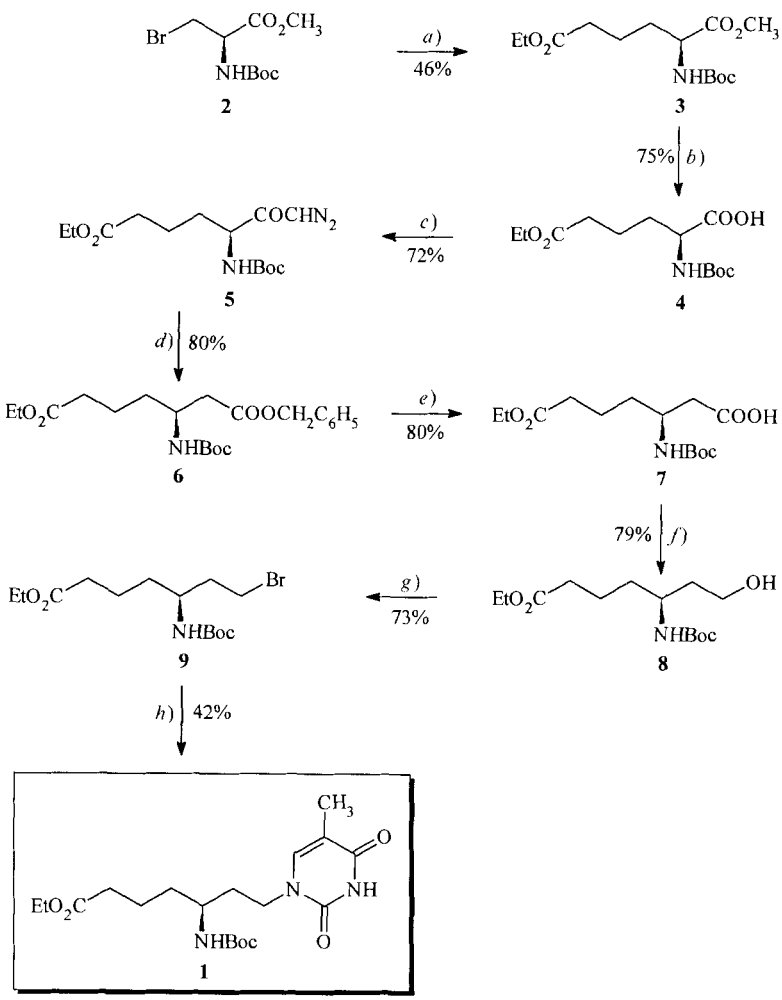


nyl]-L-serinate by treatment with CBr_4/PPh_3 [12] [13]. Vitamin-B_{12a}-catalyzed (3 mol-%) coupling of bromide **2** with ethyl acrylate in DMF, using Zn/NH_4Cl as electron and proton source, afforded the desired α-aminoadipic diester **3** in 46% yield (*Scheme 2*). As a by-product, methyl *N*-[(*tert*-butoxy)carbonyl]alaninate, arising from reduction of **2**, was identified. Lithium propanethiolate in HMPA(hexamethylphosphoramide) [14] selectively and efficiently cleaved the methyl ester function in **3** yielding the corresponding monoacid **4**.

The C_1 homologation of the α-aminoadipic-acid derivative **4** into the β-amino-acid homologue was achieved by the *Arndt-Eistert* reaction which recently proved successful in the synthesis of homopeptides [15] and carbohydrate peptidization [16]. To this end, **4** was converted to the corresponding mixed anhydride ($Et_3N/ClCO_2Et$), which was subsequently reacted with CH_2N_2 to produce the diazo ketone **5**. Treatment of **5** with PhCOOAg in the presence of Et_3N and benzyl alcohol as the nucleophile then brought about the desired *Wolff* rearrangement to give the benzyl ester **6**.

To prove the integrity of the chiral center, **6** was deprotected to the corresponding amine under mild conditions [17] and converted to the *Mosher* amide **10** [18]. ^1H- and ^{19}F-NMR (*Fig. a*) as well as HPLC analysis (see *Exper. Part*) revealed a ratio of diastereoisomers of 89:11 indicating that non-negligible racemization occurred. We did not investigate the origin of this loss in optical purity. Possible reaction steps for partial racemization are those where alanyl radicals are involved as well as the preparation of the diazo ketone **5** and the *Wolff* rearrangement. We note that the latter two steps were reported to proceed without detectable racemization in similar cases [16]. Since **6** had the consistency of a viscous oil, complete resolution of enantiomers was relegated to the stage of crystalline **1**.

Scheme 2



a) CH_2=COOEt, vitamin B_{12a}, DMF, Zn, NH_4Cl, r.t., 20 h. *b*) PrSLi, HMPT, r.t., 30 min. *c*) 1. $ClCO_2Et$, Et_3N, −15°C; 2. CH_2N_2, Et_2O, r.t. *d*) $PhCH_2OH$, PhCOOAg, Et_3N, THF, r.t. *e*) H_2, Pd/C, AcOEt, r.t., 1 h. *f*) 1. Et_3N, $ClCO_2Et$, THF; 2. $NaBH_4$, H_2O. *g*) CBr_4, PPh_3, CH_2Cl_2, 0°, 30 min. *h*) thymine, K_2CO_3, Bu_4NI, DMF, 60–70°, 3 h.

Subsequent catalytic hydrogenation of **6** in AcOEt furnished acid **7** which was further reduced to the primary alcohol **8** and finally converted to bromide **9**, the proper substrate for the introduction of the nucleobase. Thymine was chosen as the nucleobase for initial studies. Alkylation of thymine with **9** was carried out using K_2CO_3/DMF in presence of Bu_4NI according to [6]. The desired monomer building block **1** was isolated in 42% yield together with 13% of the by-product arising from N^1,N^3-bis-alkylation of thymine.

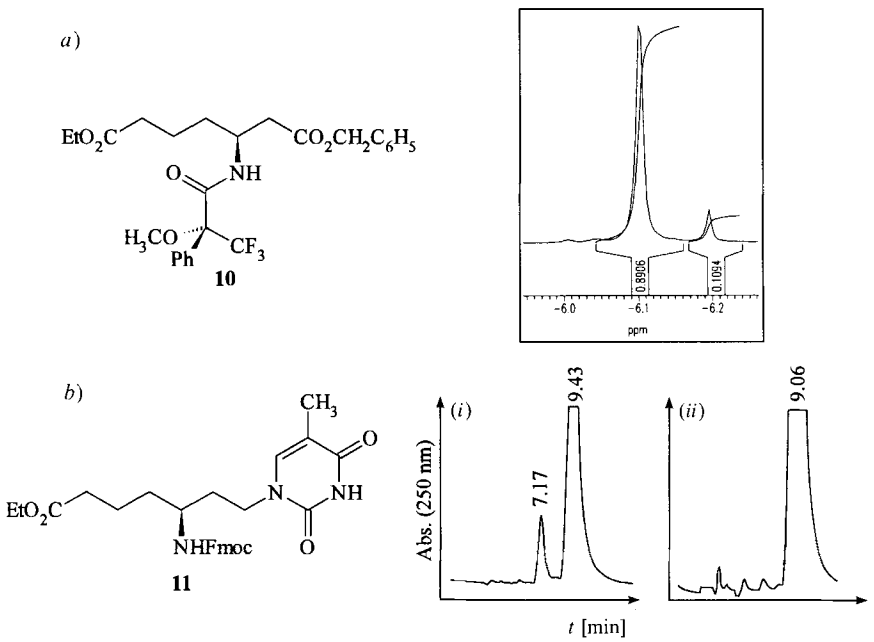


Figure. a) *^{19}F-NMR Spectrum of* Mosher *amide* **10** *and* b) *HPLC traces of* **11** *prepared from crude* (*i*) *and crystallized* **1** (*ii*)

Attempts to determine the optical purity of the monomer unit **1** itself by HPLC on a chiral stationary phase was not successful. Reasoning that aromatic residues might enhance chromatographic separability on chiral *Pirkle* stationary phases, we turned our attention to the corresponding Fmoc-protected monomer **11**. The HPLC of **11** prepared from crude **1** clearly indicated that the ratio of enantiomers was 9:1, as expected, whereas the HPLC of **11** prepared from crystallized **1** showed essentially only one peak, indicating an enantiomeric excess of > 98% (*Fig. b*). Therefore, simple crystallization of **1** removed the problem of enantiomeric impurity.

In conclusion, we found a very convenient access to the enantiomerically pure monomeric precursor **1** of the chiral and flexible nucleic-acid analog **A**. The way to oligomerization according to standard Boc-peptide solid-phase synthesis is now open.

D. S. and *C. L.* like to express here their admiration to their colleague *Rolf Scheffold* who initiated and led this project with energy, enthusiasm, and optimism up to his last day. We thank Dr. *Veronika Meier* for HPLC analyses and Dr. *Ivo Lakomy* for assistance during the phase of transition of this project. Financial support from the *Swiss National Science Foundation* is gratefully acknowledged.

Experimental Part

General. All reactions were carried out under N_2 or Ar using reagents and solvents of *puriss.* (absolute) grade from *Fluka*. THF: distilled over $K/(C_6H_5)_2CO$. Flash column chromatography (FC): commercial-grade solvents, distilled; silica gel (30–60 μm) from *Baker* (analyzed reagents). TLC: *Merck-F-254* precoated sheets, visualization by $KMnO_4/H_2O$, or vanillin/H_2SO_4, or by UV. M.p. (uncorrected): *Büchi 510*. IR: *Perkin-Elmer-FT-IR-1600*; in cm^{-1}. ^{1}H-NMR: *Bruker-AC-300* (300 MHz); δ in ppm rel. to Me_4Si (= 0 ppm), J in Hz. ^{13}C-NMR: *Bruker-AC-300* (75 MHz); δ in ppm rel. to Me_4Si (= 0 ppm), multiplicities from DEPT spectra. ^{19}F-NMR: *Bruker-DRX-400* (376 MHz); δ in ppm rel to $PhCF_3$ (= 0 ppm). MS: *Varian-MAT-CH-7A*, 70 eV; in *m/z* (%).

*Methyl 3-Bromo-*N*-[(*tert*-butoxy)carbonyl]-*L*-alaninate* (**2**). To a stirred soln. of methyl *N*-[(*tert*-butoxy)-carbonyl]-L-serinate (9.84 g, 45 mmol) and CBr_4 (18.4 g, 55 mmol) in CH_2Cl_2 (100 ml) was added portionwise at 0° Ph_3P (17.5 g, 66 mmol). Then the mixture was stirred for an additional 15–20 min, whereupon the solvent was evaporated. The residue was triturated with Et_2O (200 ml), the mixture filtered, and the filter cake washed with Et_2O (3 × 50 ml). The combined filtrate was evaporated and the residue purified by FC (hexane/AcOEt 9:1): **2** (9.2 g, 73%). White solid. TLC (hexane/AcOEt 9:1): R_f 0.2. M.p. 50–52°. IR (neat): 3400*m*, 2978*m*, 1756*s*, 1716*s*, 1504*m*, 1368*m*, 1254*w*, 1164*s*, 1066*w*, 1019*w*, 862*w*. ^{1}H-NMR ($CDCl_3$): 1.42 (*s*, 9 H); 3.65–3.93 (*m*, 5 H); 4.70–4.80 (*m*, 1 H); 5.40 (br. *m*, 1 H). ^{13}C-NMR ($CDCl_3$): 28.23 (*q*); 34.02 (*t*); 52.90 (*q*); 53.89 (*d*); 80.45 (*s*); 169.64 (*s*). MS: 283, 281 (< 1, M^+), 224 (59), 222 (58), 210 (13), 208 (12), 182 (35), 180 (29), 178 (22), 166 (15), 145 (16), 128 (30), 124 (57), 122 (58), 112 (20), 101 (30), 88 (32), 84 (40), 78 (38), 69 (16), 57 (100), 43 (46), 41 (59), 29 (45).

*6-Ethyl 1-Methyl (2*S*)-2-[(*tert*-Butoxy)carbonylamino]hexanedioate* (**3**). A suspension of Zn-dust (26.6 g, 0.41 mol) and NH_4Cl (28.6 g, 0.53 mol) in DMF (250 ml) was stirred under Ar for *ca.* 1 h. Then hydroxycobalamine hydrochloride (vitamin B_{12a}, 1.07 mmol) was added. After 15–20 min, the color of the soln. changed from red to dark green. On subsequent dropwise addition of a mixture of **2** (10 g, 35 mmol) and ethyl acrylate (9.6 ml, 89 mmol) in DMF (40 ml) during 30 min, the color shifted to dark red. The mixture was then irradiated using a 250-W halogen lamp and kept stirring at r.t. for *ca.* 20 h. After removal of DMF under vacuum, the resulting brown suspension was poured into a 25% NH_4OH soln. (50 ml) in ice-water (1 l) and extracted with Et_2O (5 × 200 ml). The org. layer was washed with H_2O (2 × 500 ml) and brine (1 × 500 ml), dried (Na_2SO_4), and evaporated. The residue was purified by FC (hexane/AcOEt 8:2): **3** (5 g, 46%). Pale yellow oil. TLC (hexane/AcOEt 7:3): R_f 0.4. IR (neat): 3370*m*, 2978*s*, 1732*s*, 1520*s*, 1454*s*, 1377*m*, 1257*m*, 1166*s*, 1028*m*, 864*w*, 780*w*. ^{1}H-NMR ($CDCl_3$): 1.19 (*t*, J = 7.2, 3 H); 1.38 (*s*, 9 H); 1.62–1.79 (*m*, 4 H); 2.24–2.28 (*m* (*t*-like), 2 H); 3.68 (*s*, 3 H); 4.06 (*q*, J = 7.2, 2 H); 4.25 (*m*, 1 H); 5.05 (br. *d*, J = 8, 1 H). ^{13}C-NMR ($CDCl_3$): 14.11 (*q*); 20.66 (*t*); 28.20 (*q*); 31.92 (*t*); 33.51 (*t*); 52.18 (*q*); 53.03 (*d*); 60.27 (*t*); 79.79 (*s*); 155.28 (*s*); 172.97 (*s*). MS: 303 (< 1, M^+), 247 (16), 244 (39), 215 (12), 202 (23), 188 (65), 184 (11), 169 (14), 158 (61), 156 (29), 145 (31), *144* (100), 124 (11), 114 (11), 99 (13), 98 (72), 88 (16), 57 (68), 56 (35), 55 (17), 41 (18).

*6-Ethyl 1-Hydrogen (2*S*)-2-[(*tert*-Butoxy)carbonylamino]hexanedioate* (**4**). A soln. of 4.6 g (15 mmol) of **3** in 30 ml of the thiolate reagent prepared from propanethiol (4 ml), LiH (1.2 g), and HMPA (40 ml) according to [14] was stirred under N_2 for *ca.* 30 min at r.t. The mixture was then transferred into ice cold 1N HCl (300 ml) and extracted with Et_2O (3 × 200 ml). After evaporation, the crude product was purified by FC (hexane/AcOEt 1:1) **4** (3.3 g, 75%). TLC (hexane/AcOEt 3:7): R_f 0.3. IR (neat): 3361*m*, 2980*m*, 1732*s*, 1520*m*, 1456*w*, 1368*m*, 1257*m*, 1166*s*, 1028*w*, 860*w*, 780*w*. ^{1}H-NMR ($CDCl_3$): 1.2 (*t*, J = 7.2, 3 H); 1.4 (*s*, 9 H); 1.68–1.85 (*m*, 4 H); 2.27–2.30 (*m* (*t*-like), 2 H); 4.08 (*q*, J = 7.2, 2 H); 4.27–4.28 (*m*, 1 H); 5.17 (br. *d*, J = 7.7, 1 H); 9.16 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 14.12 (*q*); 20.66 (*t*); 28.22 (*q*); 31.64 (*t*); 33.60 (*t*); 52.99 (*d*); 60.44 (*t*); 80.14 (*s*); 155.61 (*s*); 173.34 (*s*); 176.45 (*s*). MS: 244 (8), 233 (9), 188 (16), 145 (17), *144* (100), 143 (9), 99 (9), 98 (57), 87 (9), 59 (26), 57 (73), 56 (25), 55 (17), 43 (20), 41 (29), 29 (22).

*Ethyl (5*S*)-5-[(*tert*-Butoxy)carbonylamino]-7-diazo-6-oxoheptanoate* (**5**). To a stirred soln. of **4** (4.05 g, 14 mmol) in THF (80 ml) was added at −15° Et_3N (2.03 ml, 14.5 mmol) and ethyl chloroformate (1.38 ml, 14.5 mmol). After 15 min, a precooled, *ca.* 0.25M soln. of CH_2N_2 in Et_2O was added until the bright yellow color of the soln. persisted. The mixture was then allowed to warm up to r.t. After 2 h, the mixture was concentrated, the residue dissolved in Et_2O (100 ml), and the resulting soln. washed with sat. $NaHCO_3$ soln. (50 ml), H_2O (2 × 50 ml), dried (Na_2SO_4), and evaporated. FC (hexane/AcOEt 1:1) of the crude material afforded **5** (3.16 g, 72%). Viscous yellow oil. TLC (hexane/AcOEt 1:1): R_f 0.45. IR (neat): 3364*m*, 3096*w*, 2980*m*, 2108*s*, 1714*s*, 1642*m*, 1518*m*, 1454*w*, 1368*m*, 1250*w*, 1168*m*, 1024*w*, 862*w*. ^{1}H-NMR ($CDCl_3$): 1.17 (*t*, J = 7.2, 3 H); 1.35 (*s*, 9 H); 1.45–1.74 (*m*, 4 H); 2.25 (*td*, J = 7, 1.9, 2 H); 4.03 (*q*, J = 7.2, 2 H); 4.08–4.15 (*m*, 1 H); 5.24 (br. *d*, J = 8, 1 H); 5.45 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 14.07 (*q*); 18.2 (*d*); 20.64 (*t*); 28.16 (*q*); 31.56 (*t*); 33.5 (*t*); 56.94 (*d*); 60.25 (*t*); 79.82 (*s*); 155.35 (*s*); 172.98 (*s*); 193.74 (*s*). MS: 313 (1, M^+), 245 (22), 185 (14), 184 (26), 170 (21), 166 (12), 158 (12); 157 (36), 156 (13), 145 (12), 144 (62), 143 (50), 57 (100).

*1-Benzyl 7-Ethyl (3*S*)-3-[(*tert*-Butoxy)carbonylamino]heptanedioate* (**6**). To a stirred soln. of **5** (3.16 g, 10 mmol) and benzyl alcohol (1.35 ml, 13 mmol) in dry THF (60 ml) was added portionwise a soln. of PhCOOAg (0.655 g, 2.86 mmol) in Et_3N (9.2 ml) at r.t. After *ca.* 1 h, the dark soln. was filtered, THF evaporated, and Et_2O (100 ml) added. The Et_2O layer was washed with 1N HCl (50 ml), sat. $NaHCO_3$ soln. (50 ml), and brine (50 ml), dried (Na_2SO_4), and evaporated. FC (hexane/AcOEt 1:1) of the residue afforded **6** (3.1 g, 80%). Viscous liquid. TLC (hexane/AcOEt 1:1): R_f 0.6. IR (neat): 3370*w*, 2978*m*, 1732*s*, 1514*m*, 1456*m*, 1368*m*, 1248*w*, 1170*s*, 1028*w*, 750*w*. ^{1}H-NMR ($CDCl_3$): 1.15 (*t*, J = 7.3, 3 H); 1.35 (*s*, 9 H); 1.38–1.70 (*m*, 4 H); 2.20 (*td*, J = 7, 2.5, 2 H); 2.47 (*d*, J = 5.4, 2 H); 3.79–3.90 (*m*, 1 H); 4.03 (*q*, J = 7.3, 2 H); 4.97 (*d*, J = 9.5, 1 H); 5.02 (br. *s*, 2 H); 7.18–7.30 (*m*, 5 H). ^{13}C-NMR ($CDCl_3$): 14.0 (*q*); 21.25 (*t*); 28.13 (*q*); 33.52 (*t*); 33.63 (*t*); 39.10 (*t*); 47.14 (*d*); 59.99 (*t*); 66.12 (*t*);

78.92 (*s*); 128.02 (*d*); 128.04 (*d*); 128.32 (*d*); 135.55 (*s*); 155.11 (*s*); 171.07 (*s*); 173.00 (*s*). MS: 393 (3, M^+), 337 (19), 320 (12), 293 (33), *292* (100), 278 (11), 274 (21), 249 (10), 248 (64), 222 (62), 203 (10), 202 (71), 188 (15), 185 (13), 184 (67), 179 (19), 178 (84), 159 (10), 144 (62), 112 (10), 98 (36), 92 (23), 91 (85), 88 (15), 57 (56), 56 (11), 42 (10).

*7-Ethyl 1-Hydrogen (3S)-3-[(*tert*-Butoxy)carbonylamino]heptanedioate* (**7**). A suspension of **6** (3.1 g, 7.89 mmol) and 10% Pd/C (0.51 g) in abs. AcOEt (150 ml) was stirred under H_2 at normal pressure. After *ca.* 1 h, the mixture was filtered through *Celite* and the filtrate evaporated. The crude product was purified by FC (hexane/AcOEt 1:1): **7** (1.9 g, 80%). Colorless, viscous liquid. TLC (hexane/AcOEt 2:3): R_f 0.53. IR (neat): 3344*m*, 2926*m*, 1718*s*, 1520*m*, 1465*w*, 1368*m*, 1258*w*, 1168*s*, 1060*w*. ^{1}H-NMR ($CDCl_3$): 1.18 (*t*, J = 7.3, 3 H); 1.4 (*s*, 9 H); 1.5–1.65 (*m*, 4 H); 2.27 (*td*, J = 7.2, 2.2, 2 H); 2.51 (br. *d*, J = 4.5, 2 H); 3.76–3.86 (*m*, 1 H); 4.08 (*q*, J = 7.3, 2 H); 5.00 (br. *d*, J = 8.8, 1 H); 8.5–9.5 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 14.15 (*q*); 21.47 (*t*); 28.30 (*q*); 33.75 (*t*); 39.03 (*t*); 47.12 (*d*); 60.34 (*t*); 79.54 (*s*); 173.45 (*s*). MS: 202 (15), 184 (10), 158 (20), 144 (19), 140 (11), 132 (12), 112 (10), 101 (11), 98 (31), 88 (92), 70 (20), 59 (37), *57* (100), 56 (16), 54 (12), 44 (23), 43 (15).

*Ethyl (5S)-5-[(*tert*-Butoxy)carbonylamino]-7-hydroxyheptanoate* (**8**). Ethyl chloroformate (0.46 ml, 4.82 mmol) was added dropwise to a cooled (−15°) soln. of **7** (1.46 g, 4.82 mmol) and Et_3N (0.8 ml, 5.74 mmol) in dry THF (60 ml). The mixture was stirred at −15° for *ca.* 20 min. The resulting white precipitate was filtered and washed with THF (10 ml). The combined filtrates were then added slowly to a cooled (0°) soln. of $NaBH_4$ (0.46 g, 12 mmol) in H_2O (8 ml). After the addition, the mixture was allowed to warm up to r.t., stirred for 5 h, quenched with 1N HCl (pH *ca.* 1), and concentrated *in vacuo*. The remaining aq. soln. was extracted with CH_2Cl_2 (2 × 50 ml), the org. layer washed with sat. $NaHCO_3$ soln. and H_2O, dried (Na_2SO_4), and evaporated, and the resulting crude material purified by FC (hexane/AcOEt 1:1): **8** (1.1 g, 79%). Colorless oil. TLC (hexane/AcOEt 7:3): R_f 0.2. IR (neat): 3364*s*, 2978*s*, 1741*s*, 1662*s*, 1520*m*, 1454*w*, 1366*m*, 1250*m*, 1172*s*, 1054*w*, 864*w*. ^{1}H-NMR ($CDCl_3$): 1.16 (*t*, J = 7.2, 3 H); 1.35 (*s*, 9 H); 1.36–1.69 (*m*, 6 H); 2.23 (*td*, J = 7.2, 3, 2 H); 3.50–3.72 (*m*, 4 H); 4.03 (*q*, J = 7.2, 2 H); 4.62 (br. *d*, J = 9, 1 H). ^{13}C-NMR ($CDCl_3$): 14.08 (*q*); 21.41 (*t*); 28.21 (*q*); 33.73 (*t*); 34.73 (*t*); 38.77 (*t*); 47.01 (*d*); 58.58 (*t*); 60.21 (*t*); 79.57 (*s*); 156.98 (*s*); 173.33 (*s*). MS: M^+ not observed, 188 (10), 144 (36), 117 (16), 119 (21), 88 (63), 86 (87), *84* (100), 74 (17), 59 (12), 57 (48), 55 (10), 49 (34), 47 (40), 44 (21).

*Ethyl (5S)-7-Bromo-5-[(*tert*-butoxy)carbonylamino]heptanoate* (**9**). As described for **2**, from **8** (1.1 g, 3.82 mmol), CBr_4 (1.61 g, 4.85 mmol), and PPh_3 (1.52 g, 5.82 mmol) in CH_2Cl_2 (20 ml): **9** (0.98 g, 73%). White low melting solid after FC (hexane/AcOEt 8:2). TLC (hexane/AcOEt 7:3): R_f 0.56. IR (neat): 3358*w*, 2978*m*, 1712*s*, 1522*w*, 1463*w*, 1366*w*, 1248*w*, 1172*s*, 1036*w*. ^{1}H-NMR ($CDCl_3$): 1.20 (*t*, J = 7.2, 3 H); 1.39 (*s*, 9 H); 1.40–2.00 (*m*, 6 H); 2.27 (*td*, J = 7.2, 3, 2 H); 3.36 (*t*, J = 7.3, 2 H); 3.58–3.7 (*m*, 1 H); 4.08 (*q*, J = 7.2, 2 H); 4.38 (br. *d*, J = 9.2, 1 H). ^{13}C-NMR ($CDCl_3$): 14.18 (*q*); 21.14 (*t*); 28.31 (*q*); 29.58 (*t*); 33.76 (*t*); 34.48 (*t*); 38.95 (*t*); 49.58 (*d*); 60.27 (*t*); 79.35 (*s*); 173.28 (*s*). MS: 351 (> 1, M^+), 297 (12), 295 (12), 280 (14), 278 (15), 252 (66), 250 (63), 244 (20), 238 (18), 236 (20), 235 (10), 234 (19), 232 (17), 208 (44), 206 (45), 188 (59), 182 (29), 180 (31), 172 (24), 170 (62), 155 (22), 145 (27), *144* (100), 138 (67), 136 (67), 127 (14), 109 (23), 100 (10), 99 (10), 98 (62), 88 (30), 85 (11), 81 (21), 71 (11), 70 (11), 59 (21), 58 (13), 57 (79), 56 (39), 55 (28), 44 (15), 43 (20), 41 (31), 29 (12), 18 (25).

*(3'S)-1-{3'-[(*tert*-Butoxy)carbonylamino]-6'-(ethoxycarbonyl)hexyl}thymine* (= *Ethyl (5S)-5-[(*tert*-Butoxy)carbonylamino]-7-(1,2,3,4-tetrahydro-5-methyl-2,4-dioxopyrimidin-1-yl)heptanoate*; **1**). To a suspension of thymine (0.88 g, 6.97 mmol) in DMF (60 ml) was added anh. K_2CO_3 (0.49 g, 3.54 mmol) followed by Bu_4NI (0.2 g, 0.54 mmol). The mixture was stirred at r.t. for 30 min and then heated to 60–70° for *ca.* 30 min. A soln. of **9** (0.82 g, 2.32 mmol) in DMF was then added dropwise and stirring continued at 60–70° for 3 h. Finally the solids were filtered off, the filtrate evaporated, and the residue purified by FC (hexane/AcOEt 2:3) to give **1** (0.4 g, 42%) as a viscous oil that could be crystallized from AcOEt/hexane. M.p. 96–98° TLC (hexane/AcOEt 2:8): R_f 0.36. $[\alpha]_D^{20}$ = +12.1 (*c* = 0.01, MeOH; cryst. material). IR (neat): 3344*m*, 2978*m*, 1683*s*, 1520*m*, 1465*m*, 1366*m*, 1254*w*, 1170*m*, 1023*w*, 858*w*. ^{1}H-NMR ($CDCl_3$): 1.19 (*t*, J = 7, 3 H); 1.42 (*s*, 9 H); 1.43–1.85 (*m*, 6 H); 1.88 (*d*, J = 1.1, 3 H); 2.28 (*td*, J = 7.2, 3, 2 H); 3.48–3.62 (*m*, 2 H); 3.82–3.97 (*m*, 1 H); 4.09 (*q*, J = 7, 2 H); 4.49 (br. *d*, J = 9.5, 1 H); 7.1 (br. *s*, 1 H); 8.74 (br. *s*, 1 H). ^{13}C-NMR ($CDCl_3$): 12.26 (*q*); 14.21 (*q*); 21.16 (*t*); 28.34 (*q*); 33.75 (*t*); 34.72 (*t*); 35.11 (*t*); 46.20 (*t*); 48.11 (*d*); 60.35 (*t*); 79.65 (*s*); 110.52 (*s*); 141.10 (*d*); 150.75 (*s*); 155.83 (*s*); 164.12 (*s*); 173.28 (*s*). FAB-MS (pos.): 398 (16, $[M + H]^+$), 342 (9), 299 (23), 235 (9), 170 (12), 146 (10), 127 (20), 101 (12). Anal. calc. for $C_{19}H_{31}N_3O_6$: C 57.42, H 7.86, N 10.57; found: C 57.31, H 7.65, N 10.57.

1-Benzyl 7-Ethyl 3-{[(R)-3,3,3-Trifluoro-2-methoxy-2-phenylpropanoyl]amino}heptanedioate (**10**). CF_3COOH (0.29 ml, 3.9 mmol) was added to a stirred soln. of **6** (0.118 g, 0.3 mmol) in CH_2Cl_2 (0.62 ml, 9.6 mmol) followed by Et_3SiH (0.12 ml, 0.75 mmol), at r.t. The mixture was stirred for 30 min and then evaporated. The residue was purified by FC ($MeOH/CH_2Cl_2$ 1:10) to furnish the corresponding free amine (0.0845 g, 95%). To a soln. of this amine in CH_2Cl_2 (0.8 ml) was added the (−)-(*R*) MTPA-Cl followed by 4-(dimethylamino)pyridine (70 mg, 0.57 mmol). After 2 h stirring at r.t., the reaction was quenched with a few drops of H_2O, the mixture diluted with $CHCl_3$, and the org. phase washed with 0.1N HCl, sat. $NaHCO_3$ soln., and brine, dried (Na_2SO_4), and

evaporated: **10** (0.088 g, 64%). TLC (hexane/AcOEt 1:1): R_f 0.55. HPLC (column 3.2 mm × 25 cm, *LiChrosorb SI 60* (5 μm); hexane/i-PrOH 99:1, 1 ml/min; λ 254 nm): t_R 15.25 (89%) and 16.86 min (10.1%). IR (neat): 3350*m*, 2954*m*, 1732*s*, 1696*s*, 1520*m*, 1456*w*, 1383*w*, 1277*m*, 1178*s*, 1106*m*, 1030*w*, 716*m*, 698*m*. ^{1}H-NMR ($CDCl_3$): 1.20 (*t*, *J* = 7.3, 3 H); 1.5–1.63 (*m*, 4 H); 2.15–2.33 (*m*, 2 H); 2.59 (*d*, *J* = 5.1, 0.23 H); 2.65 (*d*, *J* = 5.1, 1.77 H); 3.32–3.36 (br. *s*, 3 H); 4.09 (*q*, *J* = 7.3, 2 H); 4.27–4.35 (*m*, 1 H); 5.12 (*s*, 2 H); 7.23–7.56 (*m*, 10 H). ^{13}C-NMR ($CDCl_3$): 14.10 (*q*); 14.13 (*q*); 21.32 (*t*); 33.05 (*t*); 33.18 (*t*); 33.45 (*t*); 33.52 (*t*); 38.47 (*t*); 45.84 (*q*); 46.10 (*s*); 54.86 (*q*); 54.9 (*q*); 60.22 (*t*); 66.48 (*t*); 66.56 (*t*); 83.72 (*s*); 121.74 (*s*); 125.58 (*d*); 127.45 (*d*); 127.47 (*d*); 128.25 (*d*); 128.27 (*d*); 128.34 (*d*); 128.42 (*d*); 128.45 (*s*); 128.54 (*d*); 129.34 (*d*); 132.65 (*s*); 135.43 (*s*); 165.85 (*s*); 170.89 (*s*); 171.02 (*s*); 172.96 (*s*). ^{19}F-NMR ($CDCl_3$): −6.1 (br. *s*, 2.67F); −6.2 (br. *s*, 0.33F). MS: 509 (1, M^+), 464 (11), 431 (10), 432 (38) 402 (10), 360 (14), 319 (38), *320* (100), 302 (13), 281 (12), 282 (72), 274 (25), 258 (10), 244 (10), 240 (15), 234 (17), 220 (16), 209 (12), 194 (16), 188 (30), 189 (90), 186 (17), 170 (25), 169 (22), 158 (13), 152 (13), 141 (15), 139 (10), 119 (15), 108 (12), 105 (22), 96 (16), 92 (38), 91 (48), 86 (37), 84 (44), 73 (16), 44 (12).

(3′S)-1-{[(3′-{9H-Fluoren-9-yl)methoxy]carbonylamino}-6′-(ethoxycarbonyl)hexyl}thymine (= *Ethyl (5S)-5-{[(9H-Fluoren-9-yl)methoxy]carbonylamino}-7-(1,2,3,4-tetrahydro-5-methyl-2,4-dioxopyrimidin-1-yl)-heptanoate*; **11**). The Boc-protected **1** (0.024 g, 0.06 mmol; non-cryst.) was deprotected as described above for **10** and the resulting amine dissolved in CH_2Cl_2 (0.5 ml). To this soln. was added at r.t. $(i\text{-}Pr)_2NEt$ (0.0075 g, 0.058 mmol) and a soln. of *N*-{[(9*H*-fluoren-9-yl)methoxy]carbonyloxy}succinimide (0.0195 g, 0.058 mmol) in CH_2Cl_2 (0.2 ml). The resulting soln. was stirred overnight at r.t. and then evaporated and the residue purified by FC (hexane/AcOEt 4:6): **11** (0.02 g, 65%). Colorless viscous liquid. TLC (hexane/AcOEt 8:2): R_f 0.2. HPLC (column 4.6 mm × 25 cm, *Chiral DNBPG-C=Si100Polyol* ((*R*)-dinitrobenzoyl-phenylglycine bonded to silica gel; 5 μm); hexane/i-PrOH 6:4, 1 ml/min; λ 254 nm): t_R 7.17 min (10.4%) and 9.43 min (89.6%). IR (neat): 3324*m*, 3073*w*, 2968*w*, 1682*s*, 1538*w*, 1450*m*, 1377*w*, 1246*m*, 1100*w*, 760*w*, 742*w*. ^{1}H-NMR ($CDCl_3$): 1.22 (*t*, *J* = 7.2, 3 H); 1.37–1.80 (*m*, 6 H); 1.9 (*s*, 3 H); 2.25–2.32 (*m*, 2 H); 3.46–3.68 (*m*, 2 H); 3.70–3.85 (*m*, 1 H); 4.09 (*q*, *J* = 7.2, 2 H); 4.17–4.25 (*m* (*t*-like), 1 H); 4.43–4.51 (*m*, 2 H); 4.84 (br. *d*, *J* = 9.2, 1 H); 7.03 (*s*, 1 H); 7.26–7.4 (*m*, 4 H); 7.57 (*d*, *J* = 7.36, 2 H); 7.73 (*d*, *J* = 7.36, 2 H); 8.86 (*s*, 1 H). ^{13}C-NMR ($CDCl_3$): 12.25 (*q*); 14.22 (*q*); 21.02 (*t*); 33.62 (*t*); 34.85 (*t*); 46.07 (*t*); 47.42 (*d*); 60.40 (*t*); 66.25 (*t*); 110.56 (*s*); 119.97 (*d*); 119.99 (*d*); 127.06 (*d*); 127.7 (*d*); 143.75 (*s*); 143.86 (*s*); 156.31 (*s*).

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