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Synthesis of protected derivatives and short peptides of antAib, a novel C^{α}-tetrasubstituted α-amino acid of the Ac_5c type possessing a fused anthracene fluorophore

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Abstract—The N^{α}-Boc and N^{α}-Fmoc protected derivatives of 2-amino-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid (antAib), a novel fluorescent, achiral, α-amino acid, rigid analogue of the known 9-antAla and 2-antAla residues, and belonging to the class of $C_i^{\alpha} \rightarrow C_i^{\alpha}$ cyclized, $C^{\alpha,\alpha}$-disubstituted glycines (strong β-turn and helix inducers in peptides), were synthesized in seven steps from 1,2,4-trimethylbenzene. The UV absorption and fluorescence properties of Boc–antAib–OEt and Boc–antAib–OH are also described. Solution syntheses of the short peptides Boc–antAib–L-Ala–OMe, Fmoc–L-Ala–antAib–L-Ala–OMe, as well as Boc–Aib–antAib–L-Ala–OMe and the side product 2,5-dioxopiperazine *cyclo*-[antAib–L-Ala], are presented as examples of the coupling ability at both C- and N-termini of the antAib residue.

1. Introduction

Fluorescence spectroscopy has become a highly valuable technique for conformational studies of biopolymers, the development of peptide-based chemosensors, and biochemical research in general.[1] Incorporation of a fluorescent probe into a peptide chain may be achieved by reaction with side-chain functional groups or the direct use of fluorophore-bearing amino acids. In this connection, *synthetic* fluorescent amino acids may exhibit significant advantages over the related *protein* (Trp, Tyr) residues in terms of potentially different and improved properties. In previous studies, we took advantage of the fluorescence, the increased rigidity, and the axial chirality of 2′,1′:1,2;1″,2″:3,4-dinaphthcyclohepta-1,3-diene-6-amino-6-carboxylic acid (Bin)[2] (Fig. 1), a $C^{\alpha,\alpha}$-disubstituted glycine derived from 1,1′-binaphthyl, to carry out photophysical studies involving intramolecular energy transfer (fluorescence quenching) and intramolecular spin polarization (CIDEP) effects in conformationally constrained peptide-based systems.[3] However, interpretation of the data was complicated by the nonplanar structure of the Bin 1,1′-binaphthyl core. To circumvent this problem, we have now designed 2-amino-2,3-dihydro-1*H*-cyclopenta-[*b*]anthracene-2-carboxylic acid (antAib), a new fluorescent α-amino acid residue which is based on a planar anthracene core and, like Bin, belongs to the class of $C_i^{\alpha} \rightarrow C_i^{\alpha}$ cyclized, $C^{\alpha,\alpha}$-disubstituted glycines (effective β-turn and helix inducers in peptides[4]). The achiral antAib residue may be regarded either as a rigid analogue of the known 9-antAla[5] (or its cyano derivative Flu[1a]) and 2-antAla[5b] residues,

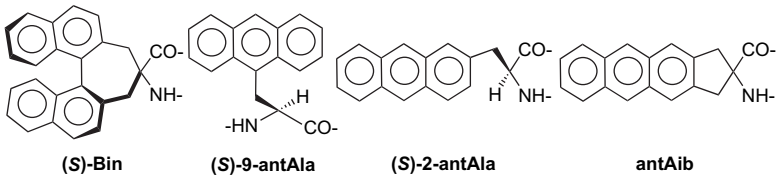

Figure 1. Chemical structure of the antAib residue compared with Bin,[2] 9-antAla,[5] and 2-antAla.[5b]

Keywords: Anthracene; Aromatic amino acid; $C^{\alpha,\alpha}$-Disubstituted glycine; Fluorescent amino acid.
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with the spatial disposition of the anthracene side-chain fluorophore relative to the α-carbon atom being completely defined, or as an anthracene-fused 1-aminocyclopentanecarboxylic acid (Ac_5c). Only quinonic derivatives of antAib have been synthesized previously by different methods.[6]

2. Results and discussion

For the synthesis of antAib, the known dimethyl anthracene-2,3-dicarboxylate **5** was used as a key intermediate. This compound was readily prepared by using an easily reproducible, published, procedure (Fig. 2),[7] in which Friedel–Crafts acylation of 1,2,4-trimethylbenzene **1** with benzoyl chloride gave the resulting benzophenone derivative **2** in 67% yield. In the second step, the two-stage oxidation of all three methyl groups present in **2** afforded the tricarboxylic acid **3** (61%), which upon cyclization in concentrated sulfuric acid formed the anthraquinone dicarboxylic acid **4** (88%). Reduction of the quinone part of **4** with activated zinc dust and ammonium hydroxide gave 2,3-anthracene dicarboxylic acid as a soft solid precipitate which could not be collected easily by filtration (see Section 3). Therefore, it was not purified, but collected by centrifugation and then directly esterified in refluxing methanol (MeOH) containing 98% H_2SO_4 to afford the dimethyl ester **5** in 71% overall yield after extraction followed by crystallization from acetone/methanol.

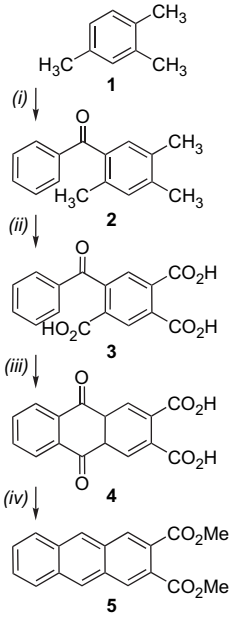

Figure 2. Synthesis of dimethyl anthracene-2,3-dicarboxylate **5**. (i) C_6H_5COCl; $AlCl_3$; 0 °C to rt; 67%. (ii) (1) 20% aq HNO_3; reflux; (2) 10% aq NaOH; $KMnO_4$; reflux; (3) H^+; 62%. (iii) 98% H_2SO_4; 120–130 °C; 87%. (iv) (1) Activated Zn powder; 20% aq NH_4OH; reflux; (2) 98% H_2SO_4; MeOH; reflux (71%).

Reduction of the diester **5** was accomplished under various experimental conditions. The expected diol was not isolated, but treated directly with acetic anhydride (Ac_2O) in pyridine[8,9] to afford the corresponding 2,3-(bis)-acetoxymethyl-anthracene **6** (Fig. 3). The use of lithium aluminum hydride in THF (tetrahydrofuran) as the reducing agent always resulted in partial over-reduction of the central ring with formation of 2,3-(bis)-acetoxymethyl-9,10-dihydroanthracene **7** along with **6**, in a ratio depending on reaction time and temperature (Table 1). Large-scale separation of the desired compound **6** from the side product **7** by chromatography was not possible because of their close R_f values (as observed by analytical TLC). However, their separation by fractional crystallization from acetone allowed the recovery of pure **6** in 46% yield from the first crop.

To transform **5** into the corresponding diol without over-reduction of the central ring, the best method we found was the use of sodium bis(2-methoxyethoxy)aluminum hydride (RedAl®) at low temperature, as proposed by Sun and Desper in a similar case.[8] Here, another side product was formed, the mono-reduced 2-acetoxymethyl-3-methyl-anthracene **8**, but in a very minor proportion relative to **6** (3% vs 86% isolated yields) when the reaction was conducted at low temperature (−15 °C to +3 °C) for a short period of time (1 h 15 min) (Table 1). Furthermore, the separation of **8** from **6** by chromatography was easy. Subsequent crystallization from boiling MeOH/CH_2Cl_2 afforded analytically pure diacetate **6** in 81% yield.

Bromuration of the diacetate **6** with HBr in acetic acid[9] readily furnished 2,3-(bis)-bromomethyl-anthracene **9** (Fig. 4) in 98% yield after crystallization from boiling MeOH/CH_2Cl_2. The dibromide **9** was then used as an electrophile for the bis-alkylation of ethyl isocyanoacetate under the phase transfer conditions developed by Kotha and Brahmachary,[6b] with potassium carbonate as a base and tetra-*n*-butylammonium ($^nBu_4N^+$) hydrogen sulfate as the catalyst, in acetonitrile at 80 °C. The resulting 2-isocyano-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid ethyl ester **10a** was not isolated, but rather the crude reaction mixture was submitted to acid hydrolysis to afford directly the desired α-amino

Table 1. Product distribution (%) after reduction of the diester **5** followed by acetylation

Reduction conditions		6	7	8
$LiAlH_4$ (THF)	0 °C to rt (2 h)	*30*[a]	*70*[a]	
$LiAlH_4$ (THF)	−14 °C to −2 °C (1 h)	*82*[a] 36[b]	*18*[a]	
$LiAlH_4$ (THF)	−60 °C to −15 °C (2 h)	*85*[a] 46[b]	*15*[a]	
RedAl® (THF)	0 °C (2 h 30 min)	54[b]		10[b]
RedAl® (THF)	0 °C (1 h 15 min)	73[b]		5[b]
RedAl® (THF)	−15 °C to +3 °C (1 h 15 min)	86[b]		3[b]

[a] Ratio determined by ^1H NMR.
[b] Isolated yield.

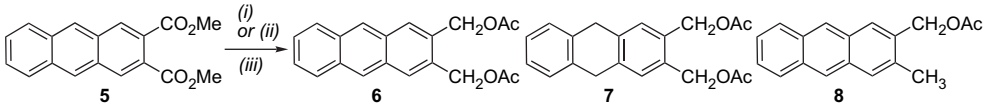

Figure 3. Reduction of the diester **5** followed by acetylation. (i) $LiAlH_4$; THF; low temperature (see Table 1). (ii) RedAl® 3.5 M in toluene; THF; low temperature (see Table 1). (iii) Ac_2O; pyridine.

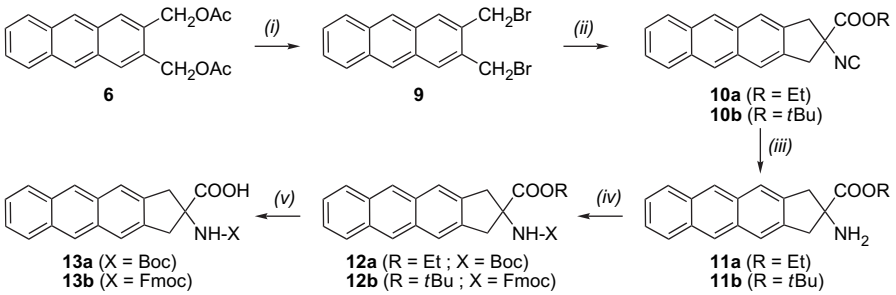

Figure 4. Synthesis of Boc–antAib–OH **13a** and Fmoc–antAib–OH **13b** from the diacetate **6**. (i) 33% HBr in AcOH; CH_2Cl_2; rt. (ii) CN–CH_2–COOEt (a series) or CN–CH_2–COO^{t}Bu (b series); K_2CO_3 or Cs_2CO_3; ^{n}Bu$_4$N$^+$, HSO_4^- (cat); CH_3CN; 80 °C. (iii) 10 N aq HCl; abs EtOH; 0 °C to rt. (iv) Boc_2O; CH_3CN; rt (a series) or Fmoc–OSu; CH_3CN/CH_2Cl_2; rt (b series). (v) 1 N NaOH; MeOH/THF; rt (a series) or TFA/CH_2Cl_2 1:2; 0 °C to rt (b series).

ester H–antAib–OEt **11a** in 28% yield after chromatography. It may be pointed out that this relatively moderate yield, due to unidentified side reactions of the dibromide **9**, is in agreement with the 29.7% yield[10] previously obtained by Kotha et al.[6b] in a similar synthesis of the parent anthraquinone-fused (instead of anthracene-fused) amino ester. Treatment of **11a** with di-*tert*-butyl dicarbonate in acetonitrile gave the fully protected derivative Boc–antAib–OEt (Boc, *tert*-butyloxycarbonyl; OEt, ethoxy) **12a** in only 37% yield after chromatography. In later runs we preferred not to isolate the α-amino ester **11a** but to perform *N*-Boc-protection directly on the crude product obtained after acid hydrolysis, thus reducing purification steps, which resulted in a slight increase in the overall yield in **12a** from **9** (18–25%). In a similar manner, the bis-alkylation of *tert*-butyl isocyanoacetate was conducted in acetonitrile at 80 °C, using cesium carbonate as a base and tetrabutylammonium hydrogen sulfate as the phase transfer catalyst, to afford 2-isocyano-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid *tert*-butyl ester **10b** in 29% yield after chromatography. Remarkably, treatment of **10b** with a few drops of concentrated hydrochloric acid (ca. 10 N) in ethanol (EtOH)/dichloromethane, from 0 °C to room temperature for a few hours (monitored by TLC) allowed the selective acidolysis of the isonitrile function without cleavage of the *tert*-butyl ester, and furnished H–antAib–O^{t}Bu (O^{t}Bu, *tert*-butoxy) **11b** in 90% yield after chromatography. Protection of the amino function of **11b** by the Fmoc (9-fluorenylmethyloxycarbonyl) group was performed using Fmoc–OSu (OSu, 1-oxysuccinimide) in dichloromethane at room temperature to afford Fmoc–antAib–O^{t}Bu **12b** in 86% yield. Finally, *C*-deprotection of **12a** by saponification of the ethyl ester function with 1 N NaOH in MeOH/THF gave Boc–antAib–OH **13a** (89–96% yield), and *C*-deprotection of **12b** by acidolysis of the *tert*-butyl ester function with TFA (trifluoroacetic acid)/CH_2Cl_2 gave **13b** (92% yield), both suitable for use in peptide synthesis.

Solution synthesis of di- and tripeptides based on antAib was carried out in order to investigate the coupling ability at both C- and N-termini of such a structurally constrained residue. Coupling of Boc–antAib–OH and HCl·L-H–Ala–OMe was performed by EDC [*N*-ethyl, *N*′-(3-dimethylaminopropyl)-carbodiimide]/HOAt (7-aza-1-hydroxy-1,2,3-benzotriazole)[11] *C*-activation to furnish Boc–antAib–L-Ala–OMe **14a** (Fig. 5) in 50–60% yield. This dipeptide was N^{α}-deprotected with TFA/CH_2Cl_2 1:3 and the resulting TFA·H–antAib–L-Ala–OMe (not isolated) was coupled with the urethane-protected *N*-carboxyanhydride (UNCA)[12] Fmoc–L-Ala–NCA, to afford the tripeptide Fmoc–L-Ala–antAib–L-Ala–OMe **15a** in 83% overall yield. These two methods are known to be efficient in difficult cases involving sterically demanding C^{α}-tetrasubstituted α-amino acids.[13] It is also interesting to note that, as previously observed in a similar case,[14] coupling of N^{α}-deprotected **14a** with the more hindered Boc–Aib–NCA (Aib, α-aminoisobutyric acid) afforded the tripeptide Boc–Aib–antAib–L-Ala–OMe **16a** in only 14% overall yield, because of a competitive cyclization to the 2,5-dioxopiperazine *cyclo*-[antAib–L-Ala] **17a**, isolated in 48% yield. One can expect therefore that in general cases where antAib is at the N-terminal position of a peptide, but not of a dipeptide methyl ester (where a fast cyclization reaction is favored), coupling at its amino function with an additional C^{α}-tetrasubstituted α-amino acid, should occur efficiently.

We have recorded the UV absorption spectra of Boc–antAib–OEt **12a** and Boc–antAib–OH **13a** and their fluorescence spectral signatures in ethanol solution. The symmetry-allowed, intense, $S_0 \rightarrow S_1$ transition of the

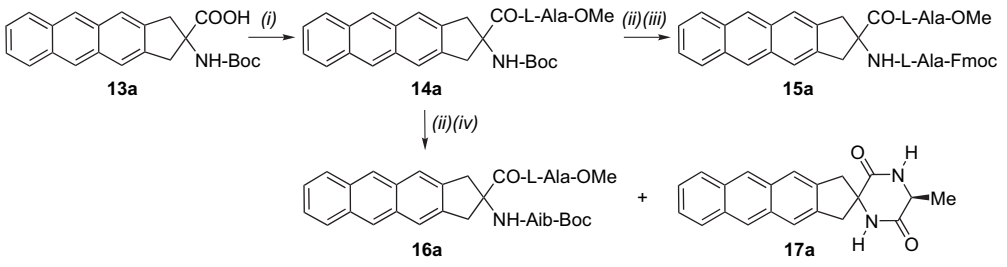

Figure 5. Solution synthesis of di- and tripeptides based on antAib. (i) HCl·H–L-Ala–OMe; NMM (*N*-methylmorpholine); EDC; HOAt; THF/CH_2Cl_2; rt. (ii) TFA/CH_2Cl_2 (1:3); 0 °C. (iii) Fmoc–L-Ala–NCA; DIEA (*N*,*N*,*N*-diisopropylethylamine); THF; 0 °C to rt. (iv) Boc–Aib–NCA; DIEA; THF; 60 °C.

anthracene chromophore is evident as a Frank–Condon vibronic progression with an origin (0,0) at 378 nm and additional peaks (0,1–0,4) separated by ca. 16 nm (λ_{max}= 359 nm)[15] (Fig. 6). The emission spectra (λ_{exc}=359 nm) have an origin at 384–385 nm, a maximum intensity at 407–408 nm, and two other peaks of the vibronic progression clearly observed at longer wavelengths (Fig. 7).

In conclusion, the syntheses of the protected derivatives Boc–antAib–OEt and Fmoc–antAib–O^{t}Bu were achieved in seven steps from 1,2,4-trimethylbenzene. Saponification of the ester function of Boc–antAib–OEt and acidolysis of Fmoc–antAib–O^{t}Bu afforded the corresponding *N*-protected amino acids, suitable for peptide elongation using either Boc or Fmoc strategies. Solution peptide syntheses of the tripeptides Fmoc–L-Ala–antAib–L-Ala–OMe and Boc–Aib–antAib–L-Ala–OMe demonstrated the coupling efficiency at both C- and N-termini of the structurally constrained antAib residue. The fluorescence spectra of Boc–antAib–OEt and Boc–antAib–OH suggest that the antAib residue may represent a novel useful spectroscopic probe in studies of peptide molecules by virtue of the appearance of its bands

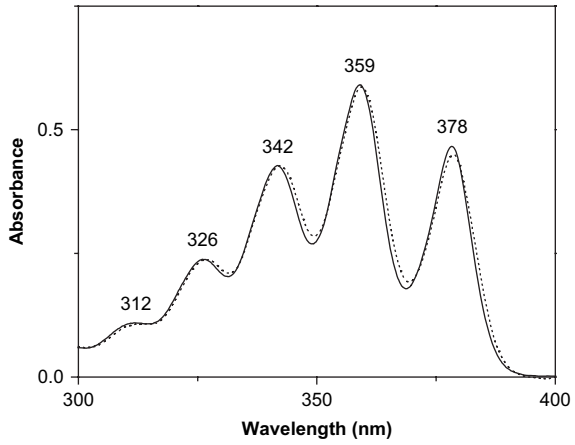

Figure 6. UV absorption spectrum (>300 nm region) of Boc–antAib–OEt **12a** (solid line) and Boc–antAib–OH **13a** (dotted line) in ethanol solution. Amino acid derivative concentration: 1×10^{-4} M.

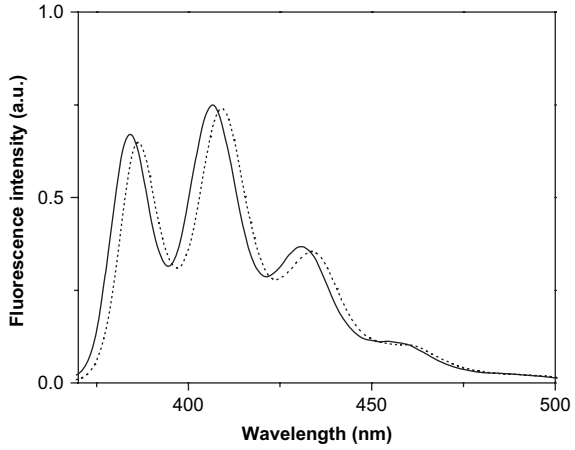

Figure 7. Fluorescence spectra in the 370–500 nm range of Boc–antAib–OEt **12a** (solid line) and Boc–antAib–OH **13a** (dotted line) in ethanol solution: λ_{exc}=359 nm. Amino acid derivative concentration: 1×10^{-6} M.

at much longer wavelengths than those typical of coded aromatic α-amino acids. To determine antAib preferred conformation, peptides based on this residue in combination with L-Ala to the hexamer level are currently being synthesized in our groups. Secondary structures involving β-turns/3_{10}-helices are expected to be efficiently induced by antAib as it is a member of the family of $C_i^{\alpha}\rightarrow C_i^{\alpha}$ cyclized, $C^{\alpha,\alpha}$-disubstituted glycines,[4] thus allowing its exploitation as a fluorophore in photophysical studies of rigid, folded, peptide architectures.

Altogether, we believe that the antAib residue will expand the scope of fluorescence analysis of peptide conformations and interactions in solution, as it represents a *unique label with frozen main-chain and side-chain rotational freedoms*, in contrast with all fluorescent probes proposed so far. That may be of main interest for the design of conformationally constrained bioactive peptide systems.[16]

3. Experimental

Melting points were measured on a Mettler apparatus with a final temperature raise of 3 °C/min or by means of a capillary tube immersed in an oil bath (Tottoli apparatus, Büchi) and are uncorrected. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker WM300 spectrometer operating at 300 MHz and 77 MHz, respectively, the solvent being used as the internal standard: $CDCl_3$ (^{1}H: δ=7.27 ppm; ^{13}C: δ=77.00 ppm), CD_3COCD_3 (^{1}H: δ=2.05 ppm; ^{13}C: δ=29.80 ppm), CD_3SOCD_3 (^{1}H: δ=2.50 ppm; ^{13}C: δ= 39.50 ppm). Splitting patterns are abbreviated as follows: (s) singlet, (d) doublet, (t) triplet, (q) quartet, (m) multiplet. Elemental analyses were performed by the C.N.R.S. Service of Microanalyses in Gif-sur-Yvette (France). Mass spectra (electrospray mode) were recorded by Vincent Steinmetz (Institut Lavoisier), and high-resolution mass spectra by Nicole Morin (Service of mass spectrometry, ENS, Paris). Analytical TLC and preparative column chromatography were performed on Kieselgel F 254 and Kieselgel 60 (0.040–0.063 mm) (Merck), respectively, with the following eluant systems: CH_2Cl_2 (I); 2.5% MeOH–97.5% CH_2Cl_2 (II); 2.5% EtOAc–97.5% CH_2Cl_2 (III); 5% EtOAc–95% CH_2Cl_2 (IV); 20% EtOAc–80% CH_2Cl_2 (V); 50% EtOAc–50% CH_2Cl_2 (VI); 5% MeOH–95% CH_2Cl_2 (VII); 10% MeOH–90% CH_2Cl_2 (VIII). UV light (λ=254 nm) allowed visualization of the spots after TLC runs for all compounds. Except when noted, all starting materials and solvents were obtained from commercial suppliers and were used as received. Fmoc–L-Ala–NCA and Boc–Aib–NCA were purchased from Fluka and Isochem, respectively.

3.1. 2,4,5-Trimethylbenzophenone (2)

A mixture of 1,2,4-trimethylbenzene **1** (20 g; 166.6 mmol) and $AlCl_3$ (23.4 g; 175 mmol) in CH_2Cl_2 (20 mL) was treated with benzoyl chloride (23.4 g; 166.5 mmol) as described in the literature,[7] to yield 24.9 g (67%) of pure **2** as a colorless liquid after vacuum distillation. Bp 152–155 °C/ca. 0.3 Torr (lit.[7] bp 130 °C/0.15 Torr). ^{1}H NMR ($CDCl_3$): δ 7.81 [m, 2H, ArH], 7.58 [m, 1H, ArH], 7.46 [m, 2H, ArH], 7.12 [s, 1H, ArH], 7.07 [s, 1H, ArH], 2.30 [s, 3H, $ArCH_3$], 2.29 [s, 3H, $ArCH_3$], 2.25 [s, 3H, $ArCH_3$].

^{13}C NMR ($CDCl_3$): δ 198.2 [C=O], 138.9, 138.0, 135.8, 134.2, 133.0, 132.5, 132.2, 129.9, 129.7, 129.1, 128.5, 128.1 [C_{Ar}], 19.35, 19.29, 18.8 [$ArCH_3$].

3.2. Benzophenone-2,4,5-tricarboxylic acid (3)

A mixture of 2,4,5-trimethylbenzophenone **2** (19.7 g; 88 mmol) and 20% HNO_3 (150 mL) was refluxed with stirring for 5 days. The resulting thick semisolid was decanted, rinsed with cold water (2×75 mL), dissolved in boiling 10% NaOH (200 mL), and treated with $KMnO_4$ (55.3 g; 350 mmol) as described in the literature,[7] to yield 17.0 g (61%) of pure **3** obtained as white crystals. Mp 224 °C (lit.[7] mp 281–283 °C). ^{1}H NMR (CD_3COCD_3): δ 8.47 [s, 1H, ArH], 7.76 [m, 2H, ArH], 7.75 [s, 1H, ArH], 7.67–7.46 [m, 3H, ArH]. ^{13}C NMR (CD_3COCD_3): δ 195.7 [C=O], 167.9, 167.4, 165.8 [COOH]; 145.5, 137.7, 137.6, 134.1, 133.8, 132.2, 131.7, 130.0, 129.4, 128.6 [C_{Ar}].

3.3. Anthraquinone-2,3-dicarboxylic acid (4)

The triacid **3** (4.20 g; 13.4 mmol) was treated with 98% H_2SO_4 (42 g) at 120–130 °C for 3 h as described in the literature,[7] to yield 3.49 g (88%) of pure **4** as a pale brown solid. Mp >300 °C (lit.[7] mp >310 °C). ^{1}H NMR (CD_3SOCD_3): δ 8.36 [s, 2H, ArH], 8.26–8.19 [m, 2H, ArH], 8.00–7.94 [m, 2H, ArH]. ^{13}C NMR (CD_3SOCD_3): δ 181.4 [C=O], 167.6 [COOH]; 137.5, 134.9, 134.2, 132.9, 127.0, 126.9 [C_{Ar}].

3.4. Dimethyl anthracene-2,3-dicarboxylate (5)

Following the literature procedure,[7] the diacid **4** (2.00 g; 6.76 mmol) was added by portions to a solution of 20% NH_4OH (100 mL) with stirring at room temperature. A clear red solution was obtained after ca. 15 min, to which was added by portions activated zinc dust (7.50 g). The resulting blood-red mixture was refluxed until the color was gone (ca. 2 h) and then filtered while hot. The solid residue was refluxed with 20% NH_4OH (50 mL) for 2 h and filtered while hot. The combined filtrates were cooled on an ice bath and then acidified to pH <1 with 10 N HCl, which resulted in the precipitation of a yellow colloidal solid which slowly settled overnight at room temperature. Attempted filtration on a Büchner was very slow and difficult. Therefore, the solid was collected by centrifugation, and then repeatedly dried by evaporation in vacuo at 50 °C after addition of methanol. The so-obtained crude anthracene-2,3-dicarboxylic acid (2.14 g) was pure by ^{1}H NMR (CD_3SOCD_3): δ 8.77 [s, 2H, ArH], 8.46 [s, 2H, ArH], 8.17–8.12 [m, 2H, ArH], 7.64–7.59 [m, 2H, ArH] with only the presence of NH_4Cl (δ 7.18 [t, J=51.0 Hz]) as contaminant. Ten similar runs starting with in total 19.25 g (65.0 mmol) of diacid **4** gave 21.80 g of such a mixture of anthracene-2,3-dicarboxylic acid and NH_4Cl. To this mixture (10.10 g) was added MeOH (400 mL) and 98% H_2SO_4 (10 mL). The resulting yellow suspension was stirred and refluxed. After ca. 1 h, a clear orange-brown solution was obtained, which was refluxed for 5 days to give a suspension again. The mixture was cooled to 0 °C, the solid was filtered, abundantly washed with MeOH, air dried (weight 6.27 g), and then dissolved in a mixture of H_2O (400 mL) and CH_2Cl_2 (600 mL) with stirring. The decanted CH_2Cl_2 solution was washed with 5% $NaHCO_3$ (100 mL), H_2O (2×400 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo to afford 5.76 g of crude diester **5** as a solid, which was pure by ^{1}H NMR and TLC. The original mother liquor (MeOH solution) was concentrated in vacuo at 40 °C to ca. 150 mL, H_2O (700 mL) added, and the mixture was extracted with CH_2Cl_2 (250 mL). The decanted CH_2Cl_2 solution was washed with 5% $NaHCO_3$ (100 mL) and H_2O (2×400 mL) as above, dried ($MgSO_4$), filtered, and evaporated in vacuo to afford 1.01 g of impure diester **5**. A second similar run starting from the remaining mixture of diacid **4** and NH_4Cl (11.70 g) gave 7.39 g of pure diester **5** after extraction of the filtered precipitate and 1.39 g of impure compound from the mother liquor. The combined pure samples of diester (13.14 g) were dissolved in boiling acetone (400 mL) and the solution concentrated to ca. 60 mL. Crystallization occurred from the boiling solution to which methanol (ca. 60 mL) was added by portions in order to increase the quantity of crystals. The mixture was concentrated again to ca. 60 mL, and then cooled to room temperature. The crystals were filtered, abundantly washed with methanol, and air dried (weight 11.96 g). More crystals (1.60 g) were obtained from the mother liquor and by repeated crystallization of the combined impure samples, to give a total of 13.56 g (71%) of analytically pure diester **5**, obtained as yellow-orange crystals. Mp 152 °C (lit.[7] mp 149–151 °C). R_f 0.18 (I). ^{1}H NMR ($CDCl_3$): δ 8.52 [s, 2H, ArH], 8.45 [s, 2H, ArH], 8.09–8.04 [m, 2H, ArH], 7.60–7.55 [m, 2H, ArH]. ^{13}C NMR ($CDCl_3$): δ 168.0 [C=O], 132.9, 131.1, 130.2, 128.2, 127.8, 127.4, 126.7 [C_{Ar}], 52.5 [OCH_3].

3.5. Reduction of dimethyl anthracene-2,3-dicarboxylate

(a) With lithium aluminum hydride: To a suspension of $LiAlH_4$ (0.190 g; 5 mmol) in THF (15 mL) magnetically stirred at 0 °C was added the diester **5** (0.294 g; 1 mmol) by portions under an argon atmosphere. The reaction mixture was stirred at room temperature for 2 h, cooled to 0 °C, and quenched by dropwise addition of saturated aqueous Na_2SO_4 (ca. 2 mL). After stirring at room temperature for 15 min, the mixture was filtered on glass wool and the filtrate was evaporated to dryness in vacuo at 40 °C. The residue was repeatedly evaporated again in vacuo after addition of methanol in order to remove water. The obtained crude product was dissolved in pyridine (10 mL) and acetic anhydride (1 mL) was added. The resulting solution was stirred at room temperature overnight and then evaporated to dryness in vacuo at 40 °C. The residue was taken up in ethyl acetate (100 mL) and 0.5 N aq HCl (100 mL) with stirring. The decanted organic phase was washed with 0.5 N aq HCl (100 mL), then with H_2O (2×100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product (0.175 g) presented a single spot on TLC with either eluant (I), (II), (III) or (IV), but contained compounds **6** and **7** in the ratio 30:70, determined by integration of their respective $ArCH_2O$ and $OCOCH_3$ singlets in ^{1}H NMR (vide infra). Preparative TLC on silica gel with eluant (III) gave 0.105 g of the same mixture **6** (30%) and **7** (70%). Fractional crystallization from a concentrated acetone solution (ca. 1 mL) gave 0.012 g (4%) of pure **6** as pale yellow crystals.

In another run, the diester **5** (0.294 g; 1 mmol) was treated by $LiAlH_4$ (0.190 g; 5 mmol) in THF (15 mL) in the same experimental conditions and workup as above, except that

the reaction was carried out at −14 °C to −2 °C for 1 h. The crude product obtained after acetylation (0.213 g) contained **6** and **7** in the ratio 82:18 by ^{1}H NMR. Fractional crystallization of this crude product from concentrated acetone (ca. 1 mL) gave 0.116 g (36%) of pure **6** as pale yellow crystals.

In another run, the diester **5** (1.470 g; 5 mmol) was treated by $LiAlH_4$ (0.950 g; 25 mmol) in THF (75 mL) in the same experimental conditions and workup as above, except that the reaction was carried out at −60 °C to −15 °C for 2 h. The crude product obtained after acetylation (1.486 g) contained compounds **6** and **7** in the ratio 85:15 by ^{1}H NMR. Fractional crystallization of this crude product from concentrated acetone (ca. 5 mL) gave 0.746 g (46%) of pure **6** as pale yellow crystals.

(b) With sodium bis(2-methoxyethoxy)aluminum hydride: To a solution of diester **5** (2.940 g; 10 mmol) in THF (100 mL) cooled to 0 °C and stirred under an argon atmosphere was added dropwise by syringe 16 mL (56 mmol) of ca. 3.5 M solution of RedAl® in toluene (Acros) over a period of 30 min. The resulting red-brown solution was stirred at 0 °C for 2 h, and then quenched by dropwise addition of aq 5% H_2SO_4 (100 mL). The mixture was poured into a separating funnel containing 5% H_2SO_4 (200 mL) and EtOAc (500 mL). After shaking and decantation, a large amount of foam at the interface between the milky yellow organic phase and the clear colorless aqueous acidic phase was present, due to the low solubility of the expected 2,3-bis(hydroxymethyl)-anthracene. The separated organic phase and the foam at the interface were washed with H_2O (500 mL), decanted, and then directly (without addition of drying agent) evaporated to dryness in vacuo. The residue was repeatedly evaporated again in vacuo after addition of methanol in order to remove water. The obtained crude product (2.454 g) was dissolved in pyridine (100 mL) and acetic anhydride (20 mL) was added. The resulting clear orange solution was magnetically stirred at room temperature for 20 h and then evaporated to dryness in vacuo at 40 °C. The residue was taken up in ethyl acetate (400 mL) and 0.5 N aq HCl (300 mL) with stirring. The decanted organic phase was washed with 0.5 N aq HCl (100 mL), then with brine (2×400 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product (3.161 g) was chromatographed on a 2.3×54 cm column of silica gel with eluant (IV) to afford the desired pure 2,3-bis(acetoxymethyl)-anthracene **6** (1.752 g; 54%) and pure 2-acetoxymethyl-3-methyl-anthracene **8** (0.272 g; 10%) as a side product.

In another run, the diester **5** (2.940 g; 5 mmol) in THF (100 mL) was treated by a 3.5 M solution of RedAl® in toluene (16 mL; 56 mmol) in the same experimental conditions and workup as above, except that the reaction was conducted at 0 °C for 15 min (addition) and then for a further 1 h. Column chromatography of the crude product obtained after acetylation (3.198 g) gave **6** (2.354 g; 73%) and **8** (0.140 g; 5%).

In another run, the diester **5** (3.633 g; 12.4 mmol) in THF (125 mL) was treated by a 3.5 M solution of RedAl® in toluene (19 mL; 66 mmol) in the same experimental conditions and workup as above, except that the reaction was conducted at −15 °C to −13 °C for 15 min (addition) and then at −13 °C to +3 °C for a further 1 h. Column chromatography of the crude product obtained after acetylation (3.917 g) gave **6** (3.437 g; 86%) and **8** (0.114 g; 3%). The pure compound **6** (3.437 g) was dissolved in boiling CH_2Cl_2 (100 mL) (water bath at 80 °C) and MeOH (50 mL) was added. The solution was concentrated to ca. 50 mL upon boiling (crystallization started to occur from the boiling solution). Methanol (50 mL) was added, the mixture was concentrated again to ca. 30 mL upon boiling, and then cooled to room temperature. The resulting crystals were filtered, abundantly washed with MeOH, and air dried to give 3.203 g (81%) of analytically pure **6**. Similar crystallization of the side product **8** (0.553 g; combined samples from several runs) from boiling MeOH (CH_2Cl_2) gave 0.384 g of yellow crystals.

3.6. 2,3-Bis(acetoxymethyl)-anthracene (6)

Yellow crystals. Mp 185 °C. R_f 0.2–0.3 (I), 0.75 (II), 0.35 (III), 0.50 (IV). ^{1}H NMR ($CDCl_3$): δ 8.43 [s, 2H, ArH], 8.04 [s, 2H, ArH], 8.04–8.00 [m, 2H, ArH], 7.53–7.48 [m, 2H, ArH], 5.39 [s, 4H, $ArCH_2O$], 2.17 [s, 6H, $OCOCH_3$]. ^{13}C NMR ($CDCl_3$): δ 170.6 [C═O], 132.2, 131.3, 130.8, 129.7, 128.2, 126.4, 125.8 [C_{Ar}], 64.6 [$ArCH_2O$], 20.9 [$OCOCH_3$]. Anal. Calcd for $C_{20}H_{18}O_4$ (322.344): C, 74.52; H, 5.63. Found: C, 74.92; H, 5.65.

3.7. 2,3-Bis(acetoxymethyl)-9,10-dihydroanthracene (7)

Not isolated. Characterized by ^{1}H and ^{13}C NMR in mixtures with **6**. R_f 0.2–0.3 (I), 0.75 (II), 0.35 (III), 0.50 (IV). ^{1}H NMR ($CDCl_3$): δ 7.36 [s, 2H, ArH], 7.32–7.27 [m, 2H, ArH], 7.25–7.20 [m, 2H, ArH], 5.22 [s, 4H, $ArCH_2O$], 3.95 [s, 4H, $ArCH_2Ar$], 2.11 [s, 6H, $OCOCH_3$]. ^{13}C NMR ($CDCl_3$): δ 170.6 [C═O], 137.4–125.7 [C_{Ar}], 63.7 [$ArCH_2O$], 35.6 [$ArCH_2Ar$], 20.9 [$OCOCH_3$].

3.8. 2-Acetoxymethyl-3-methyl-anthracene (8)

Yellow crystals. Mp 194 °C. R_f 0.70 (IV). ^{1}H NMR ($CDCl_3$): δ 8.43 [s, 1H, ArH], 8.40 [s, 1H, ArH], 8.02–7.97 [m, 2H, ArH], 7.98 [s, 1H, ArH], 7.80 [s, 1H, ArH], 7.49–7.44 [m, 2H, ArH], 5.32 [s, 2H, $ArCH_2O$], 2.55 [s, 3H, $ArCH_3$], 2.18 [s, 3H, $OCOCH_3$]. ^{13}C NMR ($CDCl_3$): δ 170.9 [C═O], 133.9, 132.5, 132.1, 131.7, 131.5, 130.3, 128.5, 128.2, 128.1, 126.2, 125.5, 125.1, 125.0 [C_{Ar}], 65.2 [$ArCH_2O$], 21.0 [$OCOCH_3$], 19.5 [$ArCH_3$].

3.9. 2,3-Bis(bromomethyl)-anthracene (9)

To a solution of diacetate **6** (3.222 g; 10 mmol) in CH_2Cl_2 (200 mL) was added a 33 wt % solution of hydrogen bromide in acetic acid (Aldrich) (20 mL; ca. 110 mmol). The solution, which became more and more turbid, was stirred at room temperature for 24 h. Water (250 mL) was added, the reaction mixture was transferred to a separating funnel, and extracted with CH_2Cl_2 (800 mL necessary for complete solubilization). The separated CH_2Cl_2 solution was washed with 5% $NaHCO_3$ (150 mL) and then H_2O (2×150 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The obtained crystalline crude product (3.680 g) was stirred in boiling CH_2Cl_2 (200 mL) but could not be totally solubilized. Methanol (50 mL) was added and the mixture was

concentrated to ca. 30 mL with almost complete crystallization occurring from the boiling solution. After cooling to room temperature, the crystals were filtered, abundantly washed with MeOH, and air dried to afford 3.573 g (98%) of analytically pure dibromide **9** as yellow crystals. Mp 225 °C. R_f 0.85 (III). ^{1}H NMR ($CDCl_3$): δ 8.39 [s, 2H, ArH], 8.04 [s, 2H, ArH], 8.03–7.99 [m, 2H, ArH], 7.53–7.49 [m, 2H, ArH], 4.95 [s, 4H, $ArCH_2Br$]. ^{13}C NMR ($CDCl_3$): δ 133.1, 132.4, 131.2, 131.0, 128.2, 126.6, 126.1 [C_{Ar}], 31.6 [$ArCH_2Br$]. HRMS (DCI^+). Calcd $[M+H]^+$ for $C_{16}H_{13}$ $^{79}Br_2$: 362.9384. Found: 362.9388. Calcd $[M+H]^+$ for $C_{16}H_{13}$ $^{79}Br^{81}Br$: 364.9364. Found: 364.9373. Calcd $[M+H]^+$ for $C_{16}H_{13}$ $^{81}Br_2$: 366.9346. Found: 366.9350. Anal. Calcd for $C_{16}H_{12}Br_2$ (364.088): C, 52.78; H, 3.32. Found: C, 52.93; H, 3.29.

3.10. 2-Isocyano-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid *tert*-butyl ester (C═antAib–O^{t}Bu 10b)

To a suspension of **9** (1.00 g; 2.75 mmol), tetrabutylammonium hydrogen sulfate (0.42 g; 1.24 mmol) and Cs_2CO_3 (5.38 g; 16.5 mmol) in CH_3CN (150 mL) was added *tert*-butyl isocyanoacetate (0.60 mL, 4.12 mmol). The mixture was stirred under argon at 75–80 °C for 48 h and then filtered through sintered glass. The filtrate was evaporated in vacuo and the residue dissolved in CH_2Cl_2 (150 mL). The organic layer was washed with water, dried over magnesium sulfate, and evaporated to dryness. The crude product was purified by column chromatography on silica gel using CH_2Cl_2 as eluant to give 0.275 g (29%) of pure **10b** as a pale yellow solid. Crystallization of an aliquot from cyclohexane/CH_2Cl_2 afforded analytically pure crystals (needles). Mp 203 °C. R_f 0.55 (I). ^{1}H NMR ($CDCl_3$): δ 8.37 [s, 2H, ArH], 8.00–7.97 [m, 2H, ArH], 7.85 [s, 2H, ArH], 7.48–7.45 [m, 2H, ArH], 3.81 and 3.61 [d, J=16.4 Hz, 2H and d, J=16.4 Hz, 2H, $ArCH_2$], 1.54 [s, 9H, CH_3 O^{t}Bu]. ^{13}C NMR ($CDCl_3$): δ 167.3 [C═O], 137.1, 131.9, 131.7, 128.3, 126.2, 125.6, 123.3 [C_{Ar}], 111.9 [C═N–], 84.3 [O–C O^{t}Bu], 77.4 [C$^\alpha$], 45.5 [$ArCH_2$], 28.0 [CH_3 O^{t}Bu]. Anal. Calcd for $C_{23}H_{21}NO_2$ (343.406): C, 80.44; H, 6.16; N, 4.08. Found: C, 80.43; H, 6.13; N, 3.88.

3.11. 2-Amino-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid ethyl ester (H–antAib–OEt 11a)

To a suspension of **9** (0.182 g; 0.5 mmol), tetrabutylammonium hydrogen sulfate (0.068 g; 0.2 mmol) and K_2CO_3 (1.38 g; 10 mmol) in CH_3CN (25 mL) was added ethyl isocyanoacetate (0.55 mL; 5 mmol). The mixture was stirred under argon at 75–80 °C for 20 h, then cooled to room temperature, and filtered through sintered glass. The solid was abundantly washed with CH_2Cl_2 and the filtrate was evaporated in vacuo. To the residue (containing C═antAib–OEt **10a**, not isolated) was added CH_2Cl_2 (10 mL), abs EtOH (25 mL) and 10 N HCl (1 mL). The mixture was magnetically stirred at room temperature for 2 h and then diluted with CH_2Cl_2 (100 mL). Water (150 mL) was added, and the mixture was made alkaline by slow addition of $NaHCO_3$ with stirring. The separated CH_2Cl_2 solution was washed with H_2O (2×100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was purified on a preparative TLC plate of silica gel with eluant (VI) to afford 0.043 g (28%) of α-amino ester **11a**. R_f 0.05 (IV); 0.20 (V). ^{1}H NMR ($CDCl_3$): δ 8.33 [s, 2H, ArH], 8.00–7.95 [m, 2H, ArH], 7.82 [s, 2H, ArH], 7.46–7.41 [m, 2H, ArH], 4.27 [q, J=7.1 Hz, 2H, CH_2 OEt], 3.71 and 3.08 [d, J=16.3 Hz, 2H, $ArCH_2$ and d, J=16.3 Hz, 2H, $ArCH_2$], 2.02 [br s, 2H, NH_2], 1.33 [t, J=7.1 Hz, 3H, CH_3 OEt]. ^{13}C NMR ($CDCl_3$): δ 172.5 [C═O], 139.8, 131.7, 131.4, 128.0, 125.5, 125.0, 122.8 [C_{Ar}], 65.4 [C$^\alpha$], 61.5 [CH_2 OEt], 45.4 [$ArCH_2$], 14.2 [CH_3 OEt]. HRMS (FAB^+) of **11a**·CF_3CO_2H. Calcd $[M+H]^+$ for $C_{20}H_{20}NO_2$: 306.1494. Found: 306.1487.

3.12. 2-Amino-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid *tert*-butyl ester (H–antAib–O^{t}Bu 11b)

The isonitrile **10b** (0.103 g; 0.300 mmol) was dissolved in CH_2Cl_2 (20 mL) and ethanol (20 mL) was added. The solution was cooled to 0 °C and 10 N HCl (0.5 mL) was added. The reaction mixture was allowed to warm to room temperature and stirred for ca. 2 h, until total hydrolysis had occurred (TLC monitoring). Water (150 mL) and CH_2Cl_2 (150 mL) were added, and the mixture was made alkaline by slow addition of a large excess of $NaHCO_3$ (0.840 g; 10 mmol) with stirring. The separated CH_2Cl_2 solution was washed with water (2×100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was chromatographed on a column of silica gel with eluant (V) to afford 0.090 g (90%) of pure **11b** as a pale yellow solid. Mp 227 °C. R_f 0.31 (V). ^{1}H NMR ($CDCl_3$): δ 8.33 [s, 2H, ArH], 8.00–7.96 [m, 2H, ArH], 7.81 [s, 2H, ArH], 7.47–7.42 [m, 2H, ArH], 3.66 and 3.05 [d, J=16.3 Hz, 2H, $ArCH_2$ and d, J=16.3 Hz, 2H, $ArCH_2$], 1.86 [br s, 2H, NH_2], 1.51 [s, 9H, CH_3 O^{t}Bu]. ^{13}C NMR ($CDCl_3$): δ 175.7 [C═O], 140.4, 131.9, 131.5, 128.2, 125.7, 125.1, 122.9 [C_{Ar}], 81.6 [O–C O^{t}Bu], 66.1 [C$^\alpha$], 45.6 [$ArCH_2$], 28.2 [CH_3 O^{t}Bu]. Anal. Calcd for $C_{22}H_{23}NO_2$ (333.412): C, 79.25; H, 6.95; N, 4.20. Found: C, 79.07; H, 6.98; N, 4.05.

3.13. 2-*tert*-Butyloxycarbonylamino-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid ethyl ester (Boc–antAib–OEt 12a)

(a) A solution of the α-amino ester **11a** (0.034 g; 0.11 mmol) and Boc_2O (0.050 g; 0.22 mmol) in CH_3CN (2 mL) was stirred at room temperature for 3 days and then evaporated in vacuo. The crude product was chromatographed on a preparative TLC plate of silica gel with eluant (III) to afford 0.0167 g (37%) of pure **12a**.

(b) In other experiments on a larger scale, without isolation/characterization of the isonitrile and α-amino ester intermediates, a mixture of dibromide **9** (0.364 g; 1 mmol), tetrabutylammonium hydrogen sulfate (0.136 g; 0.4 mmol), K_2CO_3 (2.76 g; 10 mmol), and ethyl isocyanoacetate (0.30 mL; 2.75 mmol) in CH_3CN (50 mL) was reacted in the same experimental conditions and workup as above (in Section 3.10). The crude product was submitted to direct acidic hydrolysis with 10 N HCl (1 mL) in CH_2Cl_2 (10 mL) and abs EtOH (25 mL), also as above. The crude product obtained after extraction (containing the α-amino ester **11a**) was reacted with Boc_2O (0.347 g; 1.59 mmol) in CH_3CN (5 mL) and CH_2Cl_2

(10 mL) at room temperature for 5 days and then evaporated in vacuo. The crude product was chromatographed on a 2.3×27 cm column of silica gel with eluant (III), to afford 0.102 g (25%) of pure *N*-Boc-protected α-amino ester **12a**. In another run on a larger scale, a mixture of dibromide **9** (1.820 g; 5 mmol), tetrabutylammonium hydrogen sulfate (0.678 g; 2 mmol), K_2CO_3 (13.8 g; 100 mmol), and ethyl isocyanoacetate (1.5 mL; 2.75 mmol) in CH_3CN (250 mL) was reacted in the same experimental conditions and workup as above. The crude product was submitted to direct acidic hydrolysis with 10 N HCl (10 mL) in CH_2Cl_2 (75 mL) and abs EtOH (175 mL), also as above. The crude product obtained after extraction was reacted with Boc_2O (1.816 g; 8.33 mmol) in CH_3CN (25 mL) and CH_2Cl_2 (50 mL) at room temperature for 4 days, then diluted with CH_2Cl_2 (ca. 200 mL), filtered through Celite, and evaporated in vacuo. The crude product was dissolved in CH_2Cl_2 (75 mL) and chromatographed on a 3×42 cm column of silica gel with eluant (III) to afford 0.373 g (18%) of pure **12a**. Several other runs in the same experimental conditions and workup gave a similar yield. The pure compound **12a** from several runs (0.514 g) was dissolved in CH_2Cl_2 (25 mL) and EtOAc (5 mL) was added. The clear yellow solution was concentrated under a slight vacuum at 60 °C to ca. 4 mL where crystallization started to occur. Methanol (10 mL) was added and the mixture was concentrated again to ca. 2 mL, then cooled at +4 °C for 3 h. More MeOH (10 mL) was added, the crystals were filtered, abundantly washed with MeOH, and air dried to give 0.418 g (81%) of analytically pure **12a** as a yellow solid. Another similar crystallization process starting from pure **12a** (0.722 g) gave 0.598 g of analytically pure crystals. Mp 221 °C. R_f 0.30 (III); 0.90 (V). ^{1}H NMR ($CDCl_3$): δ 8.33 [s, 2H, ArH], 7.99–7.96 [m, 2H, ArH], 7.79 [s, 2H, ArH], 7.47–7.43 [m, 2H, ArH], 5.11 [br s, 1H, NH], 4.27 [q, J=7.1 Hz, 2H, CH_2 OEt], 3.77 and 3.42 [d, J=16.9 Hz, 2H, $ArCH_2$ and br d, J=16.7 Hz, 2H, $ArCH_2$], 1.45 [s, 9H, CH_3 Boc], 1.29 [t, J=7.1 Hz, 3H, CH_3 OEt]. ^{13}C NMR ($CDCl_3$): δ 173.2 [C=O], 155.0 [C=O Boc], 139.0, 131.6, 131.4, 128.0, 125.6, 125.1, 122.6 [C_{Ar}], 80.1 [C–O Boc], 66.4 [C^{α}], 61.6 [CH_2 OEt], 43.1 [$ArCH_2$], 28.2 [CH_3 Boc], 14.1 [CH_3 OEt]. ESI$^+$ MS m/z (relative intensity): 428.3 (100) $[M+Na]^+$, 833.5 (58) $[2M+Na]^+$. HRMS (FAB$^+$). Calcd $[M]^+$ for $C_{25}H_{27}NO_4$: 405.1940. Found: 405.1953. Calcd $[M+H]^+$ for $C_{25}H_{28}NO_4$: 406.2018. Found: 406.2014. Anal. Calcd for $C_{25}H_{27}NO_4$ (405.474): C, 74.05; H, 6.71; N, 3.45. Found: C, 73.87; H, 6.95; N, 3.71.

3.14. 2-(9-Fluorenylmethoxycarbonylamino)-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid *tert*-butyl ester (Fmoc–antAib–O^{t}Bu 12b)

(a) A solution of the α-amino ester **11b** (0.120 g; 0.36 mmol) and Fmoc–OSu (0.146 g; 0.43 mmol) in CH_2Cl_2 (10 mL) was magnetically stirred at room temperature for 48 h, and then diluted with CH_2Cl_2 (100 mL). The CH_2Cl_2 solution was washed with 0.5 N HCl (100 mL), 5% $NaHCO_3$ (100 mL) and then H_2O (2×100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was chromatographed on a column of silica gel with eluant (I) to afford 0.172 g (86%) of pure **12b** as a pale yellow solid.

(b) In other experiments on a larger scale, without isolation/characterization of the isonitrile and α-amino ester intermediates, a mixture of dibromide **9** (3.64 g; 10 mmol), tetrabutylammonium hydrogen sulfate (1.53 g; 4.5 mmol), Cs_2CO_3 (3.26 g; 50 mmol), and *tert*-butyl isocyanoacetate (1.75 mL; 12 mmol) in CH_3CN (250 mL) was reacted in the same experimental conditions and workup as in Section 3.9. The crude product (containing the isonitrile **10b**) was submitted to direct acidic hydrolysis with 10 N HCl (25 drops) in CH_2Cl_2 (150 mL) and abs EtOH (75 mL), in the same experimental conditions and workup as in Section 3.11. At this stage, the crude product (containing the α-amino ester **11b**) was combined with the crude products obtained from two other similar runs in which 2.27 g (6.24 mmol) and 1.14 g (3.12 mmol) of dibromide **9** were engaged, and the mixture was purified by column chromatography on silica gel with eluant (V) to afford 1.81 g (28%) of α-amino ester **11b** containing minor impurities. This sample was treated with Fmoc–OSu (3.10 g; 9.20 mmol) in CH_2Cl_2 (400 mL) in the same experimental conditions and workup as above in Section 3.13 (a). The crude product was chromatographed on a column of silica gel with eluant (I) to afford 1.84 g (17% overall from **9**) of pure **12b** as a pale yellow solid. Mp 243 °C. R_f 0.63 (III). ^{1}H NMR ($CDCl_3$): δ 8.35 [s, 2H, ArH], 8.01–7.96 [m, 2H, ArH], 7.79 [br s, 2H, ArH], 7.73 [br d, J∼7.5 Hz, 2H, ArH Fmoc], 7.58 [d, J=7.0 Hz, 2H, ArH Fmoc], 7.48–7.43 [m, 2H, ArH], 7.38–7.24 [m, 4H, ArH Fmoc], 5.40 [br s, 1H, NH], 4.41 [br m, 2H, CH_2 Fmoc], 4.22 [m (t-like), J∼6.7 Hz, 1H, CH Fmoc], 3.72 and 3.52 [br d, J∼17.3 Hz, 2H, $ArCH_2$ and br d, J∼17.3 Hz, 2H, $ArCH_2$], 1.41 [s, 9H, CH_3 O^{t}Bu]. ^{13}C NMR ($CDCl_3$): δ 172.3 [C=O], 155.7 [C=O Fmoc], 144.1, 141.5, 139.6, 131.8, 131.6, 128.2, 127.9, 127.3, 125.8, 125.3, 125.2, 122.6, 120.2 [C_{Ar}], 82.2 [O–C O^{t}Bu], 67.4 [CH_2 Fmoc], 66.9 [C^{α}], 47.4 [CH Fmoc], 43.1 [$ArCH_2$], 28.0 [CH_3 O^{t}Bu]. HRMS (FAB$^+$). Calcd $[M+Na]^+$ for $C_{37}H_{33}NO_4Na$: 578.2307. Found: 578.2313. Anal. Calcd for $C_{37}H_{33}NO_4$ (555.642): C, 79.97; H, 5.99; N, 2.52. Found: C, 80.45; H, 6.12; N, 2.42.

3.15. 2-*tert*-Butyloxycarbonylamino-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid (Boc–antAib–OH 13a)

To a solution of **12a** (0.203 g; 0.5 mmol) in THF (20 mL) and MeOH (40 mL) was added a solution of 1 N NaOH (20 mL). The reaction mixture was magnetically stirred at room temperature for 24 h, cooled by addition of ice, acidified by addition of 0.5 N HCl (50 mL), and extracted with CH_2Cl_2 (2×250 mL). The CH_2Cl_2 solution was washed with H_2O (250 mL), filtered, and evaporated in vacuo. The residue was dried by repeated evaporation in vacuo at 40 °C after addition of methanol to afford 0.183 g (96%) of pure **13a** as a pale yellow crystalline powder. Several similar runs gave 89–96% yields. Mp >300 °C. R_f 0.03 (V); 0.10 (VI). ^{1}H NMR ($CDCl_3$/CD_3OD 4:1): δ 8.22 [s, 2H, ArH], 7.87 [m, 2H, ArH], 7.68 [s, 2H, ArH], 7.34 [m, 2H, ArH], 3.66 and 3.32 [d, J∼17.0 Hz, 2H and d, J∼17.0 Hz, 2H, Ar–CH_2], 1.32 [s, 9H, CH_3 Boc]. ^{13}C NMR ($CDCl_3$/CD_3OD 4:1): δ 175.5 [C=O], 155.6 [C=O Boc], 139.0, 131.2, 131.0, 127.5, 125.0, 124.5, 121.9 [C_{Ar}], 79.5 [C–O Boc], 65.7 [C^{α}], 42.4 [Ar–CH_2], 27.5 [CH_3 Boc]. ESI$^+$ MS m/z (relative intensity): 400.2 (100) $[M+Na]^+$, 416.2 (18) $[M+K]^+$, 777.4 (97) $[2M+Na]^+$. HRMS (FAB$^+$). Calcd $[M]^+$ for $C_{23}H_{23}NO_4$: 377.1627. Found: 377.1629. Calcd

$[M+H]^+$ for $C_{23}H_{24}NO_4$: 378.1705. Found: 378.1709. Anal. Calcd for $C_{23}H_{23}NO_4$ (377.422): C, 73.19; H, 6.14; N, 3.71. Found: C, 72.72; H, 6.55; N, 3.74.

3.16. 2-(9-Fluorenylmethoxycarbonylamino)-2,3-dihydro-1*H*-cyclopenta[*b*]anthracene-2-carboxylic acid (Fmoc–antAib–OH 13b)

To an ice-cold solution of **12b** (0.290 g; 0.52 mmol) in CH_2Cl_2 (10 mL) was added TFA (5 mL). The solution was magnetically stirred from 0 °C to room temperature for 4 h and then evaporated in vacuo. The solid residue was repeatedly taken up in CH_2Cl_2 and the suspension evaporated in vacuo at 40 °C. The crude product was dissolved in CH_2Cl_2 (150 mL necessary) with heating, the warm solution was filtered and then concentrated to ca. 50 mL under reduced pressure at 40 °C resulting in crystallization. Cyclohexane (ca. 30 mL) was added and the mixture was concentrated again to ca. 25 mL under reduced pressure. The crystals were triturated at room temperature, filtered, abundantly washed with a solution of cyclohexane/CH_2Cl_2 ca. 95:5 (v/v), and air dried to afford 0.240 g (92%) of pure **13b** as a pale yellow crystalline powder. Mp 244–246 °C. R_f 0.08 (VII), 0.42 (VIII). ^{1}H NMR ($CDCl_3$/CD_3OD 9:1 v/v): δ 8.29 [s, 2H, ArH], 7.94–7.91 [m, 2H, ArH], 7.75 [br s, 2H, ArH], 7.66 [br d, J∼7.3 Hz, 2H, ArH Fmoc], 7.51 [d, J=7.3 Hz, 2H, ArH Fmoc], 7.41–7.37 [m, 2H, ArH], 7.31 [m (t-like), J∼7.4 Hz, 2H, ArH Fmoc], 7.21 [m (t-like), J∼7.4 Hz, 2H, ArH Fmoc], 4.33 [br m, 2H, CH_2 Fmoc], 4.15 [m (t-like), J∼6.7 Hz, 1H, CH Fmoc], 3.74 and 3.46 [br d, J∼16.2 Hz, 2H, $ArCH_2$ and br d, J∼16.9 Hz, 2H, $ArCH_2$]. ^{13}C NMR ($CDCl_3$/CD_3OD 9:1 v/v): δ 175.2 [C=O], 156.0 [C=O Fmoc], 143.6, 141.1, 139.0, 131.5, 131.3, 127.9, 127.5, 126.9, 125.5, 125.0, 122.4, 119.8 [C_{Ar}], 67.1 [C^{α}], 66.6 [CH_2 Fmoc], 47.0 [CH Fmoc], 42.7 [$ArCH_2$]. ESI$^+$ MS *m/z* (relative intensity): 522.3 (100) $[M+Na]^+$, 538.3 (27) $[M+K]^+$. Anal. Calcd for $C_{33}H_{25}NO_4\cdot 0.5H_2O$ (508.546): C, 77.93; H, 5.15; N, 2.75. Found: C, 78.13; H, 5.39; N, 2.55.

3.17. Boc–antAib–L-Ala–OMe (14a)

To a suspension of **13a** (0.133 g; 0.35 mmol), HCl·L-H–Ala–OMe (0.148 g; 1.06 mmol), and HOAt (0.097 g; 0.71 mmol) in THF (3 mL) and CH_2Cl_2 (3 mL) was added NMM (0.160 mL; 1.45 mmol) and then EDC (0.102 g; 0.53 mmol). The reaction mixture was stirred at room temperature for 44 h and evaporated to dryness in vacuo. The residue was solubilized in several portions of EtOAc (total of ca. 150 mL) and 0.5 N HCl (total of ca. 100 mL) with stirring, and the solutions combined and transferred into a separatory funnel. The decanted organic phase was extracted again with 0.5 N HCl (2×50 mL), and then H_2O (100 mL), 5% $NaHCO_3$ (50 mL), and H_2O (2×100 mL), dried ($MgSO_4$), filtered and evaporated in vacuo. The crude product was chromatographed on a preparative TLC plate of silica gel with eluant (II) to afford 0.082 g (50%) of pure **14a** as a solid. Another run under similar experimental conditions and starting from 0.062 g (0.16 mmol) of **13a** gave 0.047 g (62%) of pure **14a**. Mp 226–228 °C. R_f 0.40 (II). ^{1}H NMR ($CDCl_3$): δ 8.33 [s, 2H, ArH], 7.99–7.96 [m, 2H, ArH], 7.81 [s, 1H, ArH], 7.79 [s, 1H, ArH], 7.46–7.43 [m, 2H, ArH], 7.15 [br m, 1H, NH Ala], 5.22 [s, 1H, NH antAib], 4.64 [dq, J∼7.2 Hz and 7.2 Hz, 1H, CH^{α} Ala], 3.85 [d, J∼16.7 Hz, 1H, $ArCH_A$ antAib], 3.76 [d (partly masked), J∼16.7 Hz, 1H, $ArC'H_A$ antAib], 3.52–3.36 [br m, 2H, $ArCH_B$ and $ArC'H_B$ antAib], 3.74 [s, 3H, OCH_3], 1.44 [s, 9H, CH_3 Boc], 1.43 [d (partly masked), J∼7.1 Hz, 3H, CH_3 Ala]. ^{13}C NMR ($CDCl_3$): δ 173.3, 172.3 [C=O Ala and antAib], 154.9 [C=O Boc], 139.1, 131.6, 131.4, 128.0, 125.6, 125.1, 122.9, 122.8 [C_{Ar}], 80.6 [C–O Boc], 67.5 [C^{α} antAib], 52.4 [OCH_3], 48.3 [C^{α} Ala], 42.6, 42.1 [$ArCH_2$ antAib], 28.2 [CH_3 Boc], 18.3 [CH_3 Ala]. $[\alpha]_{589}^{25}$ −16.7, $[\alpha]_{578}^{25}$ −17.3, $[\alpha]_{546}^{25}$ −19.3, $[\alpha]_{436}^{25}$ −34.0 (*c* 0.2; EtOAc). ESI$^+$ MS *m/z* (relative intensity): 485.3 (100) $[M+Na]^+$, 385.3 (40) $[M+Na\text{-}Boc]^+$, 947.6 (44) $[2M+Na]^+$. Anal. Calcd for $C_{27}H_{30}N_2O_5\cdot 0.5H_2O$ (471.534): C, 68.77; H, 6.63; N, 5.94. Found: C, 69.15; H, 6.85; N, 5.93.

3.18. Fmoc–L-Ala–antAib–L-Ala–OMe (15a)

To an ice-cold solution of dipeptide **14a** (0.109 g; 0.23 mmol) in CH_2Cl_2 (6 mL) was added TFA (2 mL). The solution was stirred at 0 °C for 3 h and evaporated in vacuo at 25 °C. The residue was repeatedly dissolved in CH_2Cl_2 and the solution evaporated in vacuo to yield crude TFA·H–antAib–L-Ala–OMe (not characterized). To this product was added THF (5 mL), the mixture was magnetically stirred at 0 °C for 10 min and DIEA (0.180 mL; 1.03 mmol) was added, followed by solid Fmoc–L-Ala–NCA (0.238 g; 0.71 mmol). The solution was stirred at room temperature for 66 h and evaporated in vacuo at 40 °C. The residue was dissolved in EtOAc by portions and the solutions combined and transferred to a separatory funnel. The organic solution (ca. 150 mL of EtOAc) was washed with 0.5 N HCl (2×75 mL), H_2O (2×100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was chromatographed on a preparative TLC plate of silica gel with eluant (II) (three consecutive elutions) to afford 0.128 g (83%) of pure **15a** as a solid. Mp 210–212 °C. R_f 0.15 (II); 0.55 (VII). ^{1}H NMR ($CDCl_3$): δ 8.22 [br s, 1H, ArH antAib], 8.15 [s, 1H, ArH antAib], 7.92–7.85 [m, 2H, ArH antAib], 7.73 [br m, 2H, ArH Fmoc], 7.70 [s, 1H, ArH antAib], 7.66 [s, 1H, ArH antAib], 7.43–7.34 [m, 6H, 2 ArH antAib and 4 ArH Fmoc], 7.29 [m (partly masked), 1H, NH Ala–OMe], 7.30–7.22 [m, 2H, ArH Fmoc], 6.95 [br s, 1H, NH antAib], 5.34 [d, J∼6.4 Hz, 1H, NH Ala–Fmoc], 4.58 [dq, J∼7.2 Hz and 7.2 Hz, 1H, CH^{α} Ala–OMe], 4.18 [m (d-like), J∼6.9 Hz, 2H, CH_2O Fmoc], 4.06 [br dq, J∼6.8 Hz and 6.8 Hz, 1H, CH^{α} Ala–Fmoc], 3.95 [br m, t-like), 1H, Ar–CH Fmoc], 3.83 [d, J∼16.8 Hz, 1H, $ArCH_A$ antAib], 3.72 [d, J∼17.1 Hz, 1H, $ArC'H_A$ antAib], 3.60 [d, J∼16.9 Hz, 1H, $ArCH_B$ antAib], 3.47 [d, J∼16.7 Hz, 1H, $ArC'H_B$ antAib], 3.66 [s, 3H, OCH_3], 1.38 [d, J=7.1 Hz, 3H, CH_3 Ala–OMe], 1.30 [d, J=6.9 Hz, 3H, CH_3 Ala–Fmoc]. ^{13}C NMR ($CDCl_3$): δ 173.3, 171.8 [C=O Ala–OMe, Ala–Fmoc and antAib], 156.5 [C=O Fmoc], 143.6, 143.4, 141.1, 138.5, 131.4, 131.3, 128.7, 128.0, 127.7, 127.0, 126.9, 125.6, 125.1, 124.9, 122.8, 122.7, 119.9 [C_{Ar}], 67.8 [C^{α} antAib], 67.1 [CH_2–O Fmoc], 52.3 [OCH_3], 50.9, 48.5 [C^{α} Ala–OMe and Ala–Fmoc], 46.8 [Ar–CH Fmoc], 42.7, 41.5 [$ArCH_2$ and $ArC'H_2$ antAib], 17.8, 17.4 [CH_3 Ala–OMe and Ala–Fmoc]. $[\alpha]_{589}^{25}$ −39.4, $[\alpha]_{578}^{25}$ −40.4, $[\alpha]_{546}^{25}$ −45.9, $[\alpha]_{436}^{25}$ −84.9 (*c* 0.11, $CHCl_3$). ESI$^+$ MS *m/z* (relative intensity): 678.3 (100) $[M+Na]^+$.

Anal. Calcd for $C_{40}H_{37}N_3O_6\cdot 0.5H_2O$ (664.728): C, 72.27; H, 5.76; N, 6.32. Found: C, 72.46; H, 5.83; N, 5.91.

3.19. Synthesis of Boc–Aib–antAib–L-Ala–OMe (16a) and *cyclo*-[antAib–L-Ala] (17a)

The dipeptide **14a** (0.043 g; 0.09 mmol) was N^{α}-deprotected in CH_2Cl_2 (3 mL) and TFA (1 mL) as above (Section 3.18). To the obtained crude TFA·H–antAib–L-Ala–OMe was added THF (3 mL), the mixture was magnetically stirred at 0 °C for 10 min and DIEA (0.065 mL; 0.37 mmol) was added, followed by solid Boc–Aib–NCA (0.085 g; 0.37 mmol). The solution was stirred at 60 °C for 21 h and evaporated in vacuo at 40 °C. The residue was stirred in the presence of EtOAc (10 mL). The residual solid was filtered, washed with EtOAc (2×10 mL), then 0.5 N HCl (2×10 mL), then H_2O (2×10 mL), and air dried to afford 0.015 g (48%) of pure **17a** as a solid, sparingly soluble in the usual organic solvents. The filtrate (mixture of EtOAc and aqueous HCl) was diluted with more EtOAc (100 mL) and transferred to a separatory funnel. The separated organic phase was washed with 0.5 N HCl (2×50 mL), H_2O (2×100 mL), dried ($MgSO_4$), filtered, and evaporated in vacuo. The crude product was chromatographed on a preparative TLC plate of silica gel with eluant (II) to afford 0.007 g (14%) of pure **16a** as a solid.

3.20. Boc–Aib–antAib–L-Ala–OMe (16a)

Mp 180–185 °C. R_f 0.25 (II). ^{1}H NMR ($CDCl_3$): δ 8.32 [s, 2H, ArH antAib], 7.99–7.96 [m, 2H, ArH antAib], 7.78 [m (s-like), 3H, 2 ArH antAib and NH Ala], 7.46–7.43 [m, 2H, ArH antAib], 6.65 [br s, 1H, NH antAib], 4.79 [s, 1H, NH Aib], 4.61 [dq, J∼7.1 Hz and 7.1 Hz, 1H, CH^{α} Ala], 4.02 [d, J∼17.0 Hz, 1H, $ArCH_A$ antAib], 3.80 [d, J∼17.0 Hz, 1H, $ArC'H_A$ antAib], 3.54 [d, J∼17.0 Hz, 1H, $ArCH_B$ antAib], 3.23 [d, J∼17.0 Hz, 1H, $ArC'H_B$ antAib], 3.73 [s, 3H, OCH_3], 1.47 [d (partly masked), J∼6.8 Hz, 3H, CH_3 Ala], 1.45 [s, 3H, CH_3 Aib], 1.42 [s, 12H, CH_3 Boc and CH_3 Aib]. ^{13}C NMR ($CDCl_3$): δ 173.5, 172.1 [C═O Ala, antAib and Aib], 155.2 [C═O Boc], 138.7, 131.5, 128.0, 125.6, 125.1, 122.7 [C_{Ar}], 81.2 [C–O Boc], 67.6 [C^{α} antAib], 57.1 [C^{α} Aib], 52.1 [OCH_3], 48.6 [C^{α} Ala], 41.2 [$ArCH_2$ antAib], 28.2 [CH_3 Boc], 26.3, 22.7 [CH_3 Aib], 17.2 [CH_3 Ala]. $[\alpha]^{25}_{589}$ −35.6, $[\alpha]^{25}_{578}$ −36.9, $[\alpha]^{25}_{546}$ −41.9, $[\alpha]^{25}_{436}$ −73.3 (*c* 0.12, $CHCl_3$). ESI$^+$ MS *m*/*z* (relative intensity): 570.4 (100) $[M+Na]^+$. Anal. Calcd for $C_{31}H_{37}N_3O_6$ (547.630): C, 67.99; H, 6.81. Found: C, 68.07; H, 7.46.

3.21. *cyclo*-[antAib–L-Ala] (17a)

Mp >300 °C. ^{1}H NMR (CD_3SOCD_3): δ 8.61 [s, 1H, NH antAib], 8.45 [s, 2H, ArH antAib], 8.27 [br s, 1H, NH Ala], 8.05–8.01 [m, 2H, ArH antAib], 7.84 [s, 1H, ArH antAib], 7.83 [s, 1H, ArH antAib], 7.48–7.44 [m, 2H, ArH antAib], 4.61 [m (q-like), J∼6.9 Hz, 1H, CH^{α} Ala], 3.72 [d, J∼17.0 Hz, 1H, $ArCH_A$ antAib], 3.61 [d, J∼17.0 Hz, 1H, $ArC'H_A$ antAib], 3.32 [d (partly masked), 1H, $ArCH_B$ antAib], 3.25 [d, J∼17.0 Hz, 1H, $ArC'H_B$ antAib], 1.34 [d, J∼6.9 Hz, 3H, CH_3 Ala]. ESI$^+$ MS *m*/*z* (relative intensity): 331.2 (100) $[M+H]^+$, 661.3 (35) $[2M+H]^+$. Anal. Calcd for $C_{21}H_{18}N_2O_2\cdot 0.3H_2O$ (335.775): C, 75.11; H, 5.58; N, 8.34. Found: C, 75.14; H, 5.58; N, 8.47.

3.22. Ultraviolet absorption and fluorescence

The electronic absorption spectra were recorded between 300 and 400 nm using a Shimadzu model UV-2501 PC spectrophotometer. The fluorescence spectra were measured between 370 and 500 nm (upon excitation at either 359 nm or 378 nm) using a Perkin Elmer model LS-50B spectrofluorimeter. Ethanol (99.8%) was purchased from Fluka.

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