Synthesis of Linearly and Angularly Fused Indane-Based Constrained α-Amino Acid Derivatives

Sambasivarao Kotha,* Nimita Gopal Krishna, Shilpi Misra, Priti Khedkar

Department of Chemistry, Indian Institute of Technology-Bombay, Mumbai 400076, India
Fax +91(22)25767152; E-mail: srk@chem.iitb.ac.in

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Abstract: The benzocyclobutene-based α-amino acid derivative, ethyl 5-acetamido-2,4,5,6-tetrahydro-1*H*-cyclobuta[*f*]indene-5-carboxylate is synthesized via coupling of a benzocyclobutene-derived dibromide with ethyl isocyanoacetate as the key step, followed by hydrolysis and subsequent acetylation. This methodology is generalized in order to prepare various linearly and angularly fused indane-based α-amino acid derivatives.

Key words: α-amino acids, [2+2+2] cycloaddition, indane-based α-amino acid, benzocyclobutene, ethyl isocyanoacetate, diversity-oriented approach

Constrained α-amino acid derivatives play an important role in the design of peptide drugs and peptidomimetics.[1] In this respect, indane-based α-amino acid **2**, which is regarded as a constrained analog of phenylalanine (**1**), is an important target (Figure 1). There are several drugs which possess an indane ring as the core structural unit,[2] and indane-related compounds have been used as ligands for asymmetric synthesis.[3] We have undertaken a program to design various indane derivatives using novel methods such as [2+2+2] cycloaddition, [4+2] cycloaddition, Suzuki–Miyaura cross-coupling and metathesis as key steps.[4–9] However, there is a need to assemble highly functionalized indane-based α-amino acid derivatives with intricate side chains. To expand the building-block approach toward indane ring systems, herein, we report the synthesis of linearly and angularly fused indane-based α-amino acid derivatives.

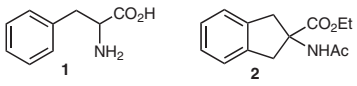

Figure 1 Phenylalanine (**1**) and indane-based α-amino acid **2**

In view of the varied applications of benzocyclobutene in organic and polymer synthesis, it occurred to us that α-amino acid derivatives containing a benzocyclobutene unit might provide the opportunity to design a library of α-amino acids suitable for post-translational peptide modifications.[10] To this end, we previously prepared benzocyclobutene-based α-amino acid derivatives **3** and **4** (Figure 2).[11] For this work, we envisaged indane-based α-amino acid derivative **5**, which contains a benzocyclobutene moiety, a worthy target. This material has the potential to undergo ring-opening of the benzocyclobutene unit to generate various polycyclic α-amino acid derivatives by adopting a Diels–Alder strategy.

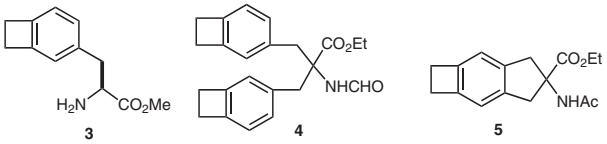

Figure 2 α-Amino acid derivatives containing a benzocyclobutene moiety

Toward the synthesis of benzocycloalkane-based α-amino acid derivative **9**, the required dibromo precursor **8** could be prepared by [2+2+2] cycloaddition[12] or bromomethylation of the parent benzocycloalkane derivative **7**.[13] In connection with the synthesis of angularly fused constrained α-amino acid derivatives **12** and **15**, the required dibromo precursors **11** and **14** can be assembled via benzylic bromination of the corresponding dimethyl derivatives **10** and **13** (Scheme 1).

The benzocyclobutene-derived dibromide **20** was prepared using our previously reported method (Scheme 2).[12] The two ester groups in compound **18**[14] were reduced to give diol **19** which underwent subsequent dibromination to afford **20**. Under bromomethylation conditions, the strained cyclobutane ring present in benzocyclobutene (**21**) undergoes ring-opening in the presence of hydrogen bromide (Scheme 2).[15a,b,d] Therefore, sodium bromide and boron trifluoride–diethyl ether complex[15c] were employed to generate benzocyclobutene-derived dibromide **20** from **19**. An alternative approach to dibromide **20** involves benzylic bromination of **23** in which there are two sets of competing benzylic positions available for radical bromination. In this context, regiochemical benzylic bromination was not a trivial exercise.

Initially, the [2+2+2] cycloaddition strategy was used to synthesize benzocycloalkane-based dibromides **20** and **24–26** via three-step sequences.[12] However, we adopted a bromomethylation protocol (Scheme 1)[13] involving a shorter route to generate the dibromo derivatives **24** and **25** since the parent hydrocarbons (indane and tetralin) are commercially available. Naphthalene dibromide **11**[16] and phenanthrene dibromide **14**[17] were prepared via benzylic

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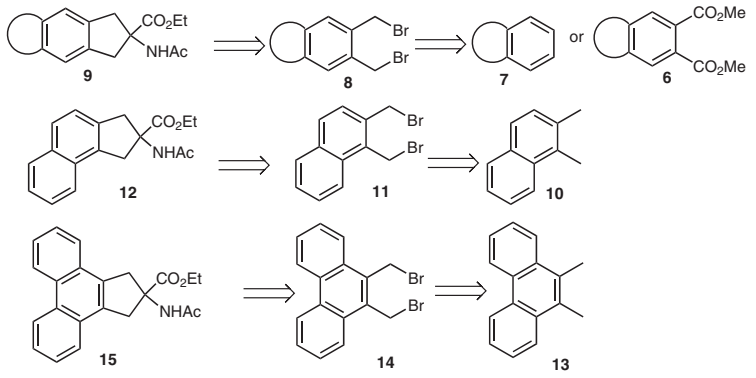
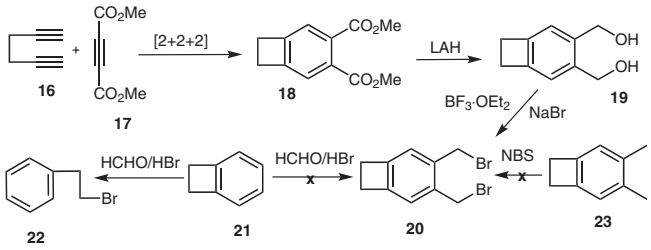


Scheme 1 Retrosynthetic approaches to linearly and angularly fused indane-based α-amino acid derivatives



Scheme 2 Preparation of benzocyclobutene-derived dibromide **20**

bromination of the corresponding dimethyl derivatives **10** and **13** under radical bromination conditions.

Having obtained the desired dibromides **20** and **24**–**26**, the next step was their alkylation with ethyl isocyanoacetate (EICA) (**27**)[18] in the presence of potassium carbonate and tetrabutylammonium hydrogen sulfate (TBAHS) as a phase-transfer catalyst in acetonitrile to give the corresponding isonitrile derivatives **28**–**31** (Scheme 3).

Attempts to purify unstable isonitrile derivatives **28** and **31** by silica gel column chromatography resulted in very low yields of the product due to decomposition. Therefore, it was decided to avoid purification of isonitrile derivatives **28** and **31** and proceed with the crude material. We were successful in isolating the isonitriles **29**, **30** and **40** by column chromatography (Schemes 3 and 4). Subsequent hydrolysis of the isonitrile derivatives with dilute hydrochloric acid in ethanol delivered the corresponding amino esters **32**–**35**, which upon protection with acetic anhydride in the presence of 4-(*N*,*N*-dimethylamino)pyridine in dichloromethane gave the corresponding *N*-acetyl derivatives **5** and **36**–**38**.

The structure of benzocyclobutene-based α-amino acid **5** was established by comparison of ^{13}C NMR spectroscopic data with those of benzocyclobutane (**21**) and adduct **39** (Figure 3).[11]

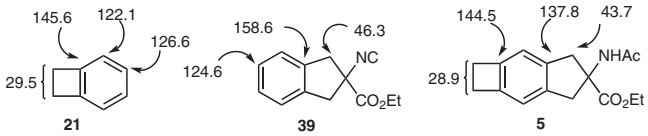
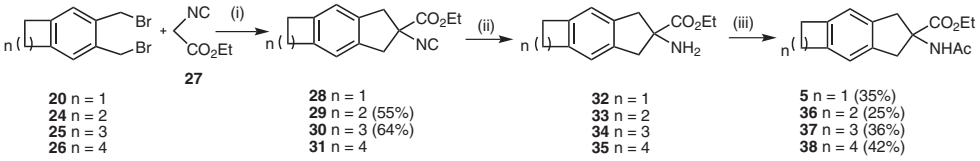


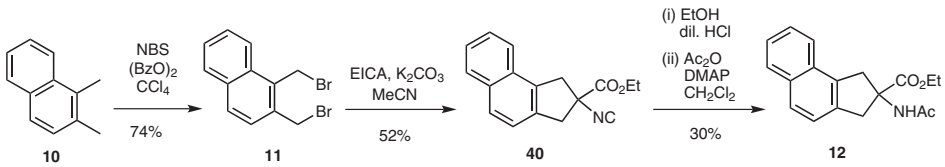
Figure 3 Comparison of the ^{13}C NMR spectroscopic data of structurally similar benzocyclobutenes

Angularly fused indane-based α-amino acid derivative **12** and phenanthrene-based α-amino acid **15** were assembled under similar reaction conditions using ethyl isocyanoacetate as a glycine equivalent (Schemes 4 and 5). Naphthalene dibromide **11** was prepared by benzylic bromination of 1,2-dimethylnaphthalene (**10**) (Scheme 4).[16]

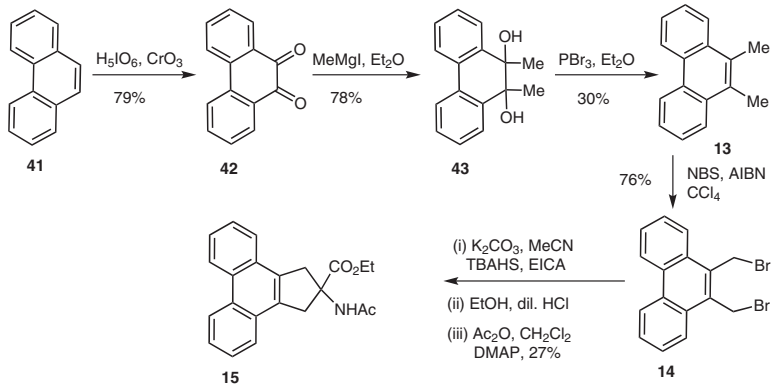
Phenanthrene dibromide **14** was prepared via a four-step sequence starting from phenanthrene (**41**). The required phenathrene-9,10-quinone (**42**) was prepared by oxida-



Scheme 3 Synthesis of linearly annulated indane-based α-amino acid derivatives. *Reagents and conditions*: (i) K_2CO_3, TBAHS, MeCN, reflux, 12–20 h; (ii) EtOH, dil. HCl, r.t., 12 h; (iii) Ac_2O, DMAP, CH_2Cl_2, r.t., 12–24 h.



Scheme 4 Synthesis of angularly fused indane-based α-amino acid derivative **12**

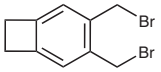
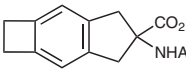
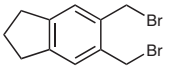
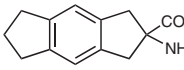
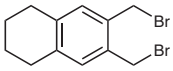
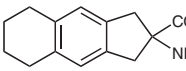
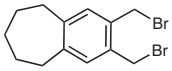
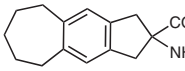
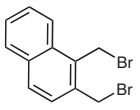
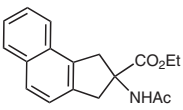
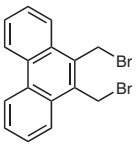
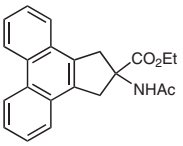


Scheme 5 Synthesis of phenanthrene-based α-amino acid derivative **15**

tion of **41**. Next, Grignard addition with methylmagnesium iodide followed by treatment with phosphorus tribromide gave 9,10-dimethylphenanthrene (**13**) (Scheme 5).[17] Phenanthrene dibromide **14** was obtained by benzylic bromination under radical bromination conditions.

Coupling of dibromides **11** and **14** with ethyl isocyanoacetate, followed by hydrolysis and acetylation gave the corresponding α-amino acid derivatives **12** and **15**, respectively. The structures of the various aromatic dibromides that underwent cyclization with ethyl isocyanoacetate and the corresponding final linearly annulated and angularly fused indane-based α-amino acid products are shown in Table 1.

Table 1 Structures of the Aromatic Dibromides and Corresponding Linearly and Angularly Fused Indane-Based α-Amino Acid Derivatives Prepared in this Work

Entry	Dibromide		Product		Yield (%)[a]
1	**20**		**5**		35
2	**24**		**36**		25
3	**25**		**37**		36
4	**26**		**38**		42
5	**11**		**12**		30
6	**14**		**15**		30

[a] Yield of compounds **5**, **38** and **15** after three steps and for compounds **36**, **37** and **12** after two steps.

In summary, we have synthesized various difficult-to-access benzocycloalkane-based α-amino acid derivatives using ethyl isocyanoacetate as a glycine equivalent for introduction of the α-amino acid moiety. The α-amino acid derivatives prepared here may find useful applications in bioorganic and medicinal chemistry.

Ethyl isocyanoacetate was prepared following the literature method.[18] Melting points were recorded on Labhosp or Veego instruments. The reaction temperatures quoted refer to those of the heating/cooling bath. IR spectra were recorded on a Nicolet Impact-400 FT IR spectrometer in KBr, $CHCl_3$ or CCl_4. ^{1}H NMR (300 and 400 MHz) and ^{13}C NMR (100.6 MHz) spectral data were obtained at room temperature on a Varian VXR 300 or an AX 400 Mercury Plus spectrometer. $CDCl_3$ was used as the solvent. Coupling constants (J) are provided in Hz. High-resolution mass measurements were carried out using a Micromass Q-Tof spectrometer. Analytical TLC was performed on glass plates (10 × 5 cm) coated with Acme silica gel, GF 254 (containing 13% $CaSO_4$ as a binder). Silica gel was coated on glass plates using a 'Sandwich Technique'. Flash chromatography was performed on Acme silica gel (100–200 mesh). Petroleum ether (PE) refers to the fraction boiling in the 60–80 °C range.

5,6-Bis(bromomethyl)-2,3-dihydro-1*H*-indene (24)

To a stirred soln of indane (2.6 mL, 21.15 mmol) in glacial AcOH (15 mL) was added paraformaldehyde (6.35 g, 212 mmol) and the resulting suspension allowed to cool to 0 °C. Next, HBr (33 wt% in glacial AcOH, 12.2 mL, 211 mmol) was added in one portion. After stirring at 0 °C for 15 min, the mixture was allowed to warm to r.t. and then heated at reflux temperature (80 °C) for 8 h. The reaction mixture was poured into ice-cold H_2O (20 mL) and neutralized with sat. aq $NaHCO_3$ (15 mL). The aq layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extract washed with H_2O (3 × 20 mL) and brine (20 mL), then dried over anhyd Na_2SO_4 to deliver the crude product as a brown oil which was purified by silica gel column chromatography (eluent: PE). The dibromide **24** was obtained as colorless needle-like crystals (2.94 g, 46%) along with the corresponding monobromide (1.54 g, 24%). The spectroscopic data of **24** were found to be identical to those of the material obtained via the [2+2+2] cycloaddition route.[12]

Mp 78–82 °C (Lit.[13] 80–82 °C); R_f = 0.3 (PE).

IR (thin film): 3054, 2304, 1618, 1421, 1265, 739 cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.03–2.11 (quin, J = 7.6 Hz, 2 H, CH_2), 2.88 (t, J = 7.6 Hz, 4 H, CH_2), 4.66 (s, 4 H, CH_2Br), 7.22 (s, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 25.3, 30.9, 32.5, 126.9, 134.3, 145.9.

6,7-Bis(bromomethyl)-1,2,3,4-tetrahydronaphthalene (25)

To a mixture of tetralin (3 mL, 22 mmol) and paraformaldehyde (5.45 g, 180 mmol) were added rapidly glacial AcOH (25 mL) and HBr (33 wt% in glacial AcOH, 10.2 mL, 176 mmol) at 0 °C. After stirring the mixture at 0 °C for 15 min, it was brought to r.t. and then heated at reflux temperature (80 °C) for 18 h. The reaction mixture was quenched by pouring into ice-cold H_2O (15 mL) and neutralized with sat. aq $NaHCO_3$ (25 mL). The aq layer was extracted with EtOAc (3 × 50 mL), dried over anhyd Na_2SO_4 and concd. The crude residue was purified by silica gel column chromatography (eluent: PE) to give the desired compound **25** as a white solid (2.90 g, 41%).

Mp 132–134 °C (Lit.[12a] 138–140 °C); R_f = 0.32 (PE).

IR (thin film): 3053, 2933, 2305, 1614, 1432, 1265, 740 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.75–1.80 (m, 4 H, CH_2), 2.83–2.86 (m, 4 H, CH_2), 4.48 (s, 4 H, CH_2Br), 7.15 (s, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 22.9, 28.9, 30.5, 131.9, 133.6, 139.1.

Coupling of Dibromo Derivatives with Ethyl Isocyanoacetate; General Procedure

To a stirred suspension of K_2CO_3 (6 mmol), TBAHS (1 mmol) and ethyl isocyanoacetate (1 mmol) in anhyd MeCN (15 mL) was added the aromatic dibromide (1 mmol). The resulting heterogeneous mixture was stirred at 75 °C for 10–20 h under N_2. Following completion of the reaction (TLC monitoring), the mixture was cooled and filtered through Celite. The filtrate was evaporated under reduced pressure and the residue used in the next step without purification. However, in some cases, the isonitrile derivative was found to be stable and could be purified and characterized from its spectral data.

Hydrolysis of the Isonitrile Derivative; General Procedure

To a soln of the isonitrile derivative in absolute EtOH (10 mL) was added dil. HCl (1 mL) dropwise and the mixture stirred at r.t. for 12 h. The EtOH was evaporated under reduced pressure and the residue dissolved in H_2O (20 mL). The aq layer was made basic (pH ~9–10) by addition of NH_3 soln and was then extracted with EtOAc (3 × 15 mL). The combined organic extract was washed with H_2O (2 × 20 mL) and brine (20 mL) and then dried over anhyd Na_2SO_4. Removal of the solvent under reduced pressure gave the required amino ester.

Acetylation of the Amino Ester; General Procedure

The amino ester was dissolved in anhyd CH_2Cl_2 (20 mL) and then DMAP (1 mmol) and freshly distilled Ac_2O (0.5 mL) were added. The mixture was stirred at r.t. for 12–24 h and then quenched by the addition of H_2O (25 mL). The aq layer was extracted with EtOAc (3 × 15 mL) and the combined organic extract washed with H_2O (2 × 10 mL) and brine (10 mL) and then dried over anhyd Na_2SO_4. The solvent was evaporated under reduced pressure and the crude residue purified by silica gel column chromatography.

Ethyl 2-Isocyano-1,2,3,5,6,7-hexahydro-*s*-indacene-2-carboxylate (29)

To a stirred suspension of K_2CO_3 (734 mg, 5.31 mmol), TBAHS (300 mg, 0.88 mmol) and ethyl isocyanoacetate (100 mg, 0.88 mmol) in anhyd MeCN (15 mL) was added dibromide **24** (269 mg, 0.88 mmol). The resulting mixture was stirred at reflux temperature. Following completion of the reaction (12 h, TLC monitoring), the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 4% EtOAc–PE) to afford the isonitrile derivative **29** as a white crystalline material (125 mg, 55%).

Mp 88–90 °C; R_f = 0.40 (10% EtOAc–PE).

IR (thin film): 2141, 1744 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.35 (t, J = 3.7 Hz, 3 H, OCH_2CH_3), 2.07–2.09 (m, 2 H, CH_2), 2.87 (t, J = 7.4 Hz, 4 H, CH_2), 3.40 (ABq, J = 15.9 Hz, 2 H, CH_2), 3.65 (ABq, J = 15.9 Hz, 2 H, CH_2), 4.31 (q, J = 3.7 Hz, 2 H, OCH_2CH_3), 7.08 (s, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1, 25.9, 32.8, 45.9, 63.1, 68.4, 120.6, 135.9, 144.2, 158.4, 169.8.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{16}H_{18}NO_2$: 256.1338; found: 256.1334.

Ethyl 2-Isocyano-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta[*b*]naphthalene-2-carboxylate (30)

To a stirred suspension of K_2CO_3 (734 mg, 5.31 mmol), TBAHS (300 mg, 0.88 mmol) and ethyl isocyanoacetate (100 mg, 0.88 mmol) in anhyd MeCN (15 mL) was added dibromide **25** (279.7 mg, 0.88 mmol). The resulting mixture was stirred at reflux temperature. Following completion of the reaction (20 h, TLC monitoring), the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 4% EtOAc–PE) to afford the isonitrile derivative **30** as a white crystalline material (152 mg, 64%).

Mp 62–64 °C; R_f = 0.35 (10% EtOAc–PE).

IR (thin film): 2139, 1746 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.34 (t, J = 3 Hz, 3 H, OCH_2CH_3), 1.83 (m, 4 H, CH_2), 2.75 (s, 4 H, CH_2), 3.44 (ABq, J = 15.9 Hz, 2 H, CH_2), 3.63 (ABq, J = 16.5 Hz, 2 H, CH_2), 4.32 (q, J = 3 Hz, 2 H, OCH_2CH_3), 6.96 (s, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.1, 23.4, 29.7, 46.4, 63.2, 68.5, 125.2, 135.3, 136.8, 158.3, 169.0.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{17}H_{20}NO_2$: 270.1494; found: 270.1494.

Ethyl 2-Isocyano-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-2-carboxylate (40)

To a stirred suspension of K_2CO_3 (220 mg, 1.6 mmol), TBAHS (108 mg, 0.32 mmol) and ethyl isocyanoacetate (36 mg, 0.32 mmol) in anhyd MeCN (10 mL) was added dibromide **11** (100 mg, 0.32 mmol). The resulting mixture was stirred at reflux temperature. Following completion of the reaction (10 h, TLC monitoring), the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 3.5% EtOAc–PE) to afford the isonitrile derivative **40** as a white crystalline material (44 mg, 52%).

Mp 77–80 °C; R_f = 0.40 (10% EtOAc–PE).

IR (thin film): 2142, 1746, 1606, 1551, 1422, 1266, 741 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 3.67 (ABq, J = 16.2 Hz, 2 H, CH_2), 3.95 (ABq, J = 16.2 Hz, 2 H, CH_2), 4.35 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.37 (d, J = 7.1 Hz, 1 H, ArH), 7.47–7.56 (m, 2 H, ArH), 7.70 (d, J = 7.9 Hz, 1 H, ArH), 7.79 (d, J = 8.3 Hz, 1 H, ArH), 7.89 (d, J = 7.9 Hz, 1 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 45.5, 47.5, 63.4, 122.6, 123.9, 125.9, 126.9, 128.8, 128.9, 130.0, 133.3, 133.7, 135.3, 168.9.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{17}H_{16}NO_2$: 266.1181; found: 266.1179.

Ethyl 5-Acetamido-2,4,5,6-tetrahydro-1*H*-cyclobuta[*f*]indene-5-carboxylate (5)

To a soln of isonitrile derivative **28** (crude reaction mixture) (116 mg, 0.48 mmol) in absolute EtOH (10 mL) was added dil. HCl (5–6 drops). After completion of the hydrolysis (ca. 12 h), the mixture was worked up according to the general procedure. The amino ester obtained was used in the next step without purification. To a soln of

the crude amino ester (100 mg, 0.43 mmol) in anhyd CH_2Cl_2 (20 mL) were added DMAP (52.4 mg, 0.43 mmol) and freshly distilled Ac_2O (0.04 mL) at r.t., and the resulting mixture stirred for 12 h. After completion of the reaction, the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 30% EtOAc–PE) to afford protected amino ester **5** as a white solid (25 mg, 35% over three steps).

Mp 144–146 °C; R_f = 0.31 (30% EtOAc–PE).

IR (thin film): 3437, 1735, 1676, 1265 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 1.94 (s, 3 H, $NHCOCH_3$), 2.08 (s, 2 H, CH_2CH_2), 3.10 (s, 2 H, CH_2CH_2), 3.19 (ABq, J = 16.4 Hz, 2 H, CH_2), 3.59 (ABq, J = 16.4 Hz, 2 H, CH_2), 4.12 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.06 (s, 1 H, $NHCOCH_3$), 6.91 (s, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 23.2, 28.9, 43.7, 61.7, 65.8, 119.4, 137.8, 144.5, 170.3, 173.0.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{16}H_{20}NO_3$: 274.1443; found: 274.1431.

Ethyl 2-Acetamido-1,2,3,5,6,7-hexahydro-*s*-indacene-2-carboxylate (36)

To a soln of isonitrile derivative **29** (100 mg, 0.39 mmol) in absolute EtOH (10 mL) was added dil. HCl (5–6 drops). After completion of the hydrolysis (ca. 12 h), the mixture was worked up according to the general procedure. The amino ester obtained was used in the next step without purification. To a soln of the crude amino ester (90 mg, 0.36 mmol) in anhyd CH_2Cl_2 (20 mL) were added DMAP (44 mg, 0.36 mmol) and freshly distilled Ac_2O (0.5 mL) at r.t. After completion of the reaction (24 h, TLC monitoring), the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 20% EtOAc–PE) to afford *N*-acetyl derivative **36** as a colorless liquid (28 mg, 25% over two steps).

R_f = 0.24 (30% EtOAc–PE).

IR (neat): 3430, 2964, 1742, 1652, 1260, 1023 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.94 (s, 3 H, $NHCOCH_3$), 2.07 (t, J = 7.3 Hz, 4 H, CH_2), 2.84–2.89 (m, 2 H, CH_2), 3.14 (ABq, J = 16.5 Hz, 2 H, CH_2), 3.59 (ABq, J = 16.5 Hz, 2 H, CH_2), 4.22 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 6.04 (s, 1 H, $NHCOCH_3$), 7.06 (s, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 23.3, 25.9, 32.7, 43.3, 61.7, 66.5, 120.7, 137.8, 143.6, 170.4, 173.0.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{17}H_{22}NO_3$: 288.1600; found: 288.1608.

Ethyl 2-Acetamido-2,3,5,6,7,8-hexahydro-1*H*-cyclopenta[*b*]naphthalene-2-carboxylate (37)

To a soln of isonitrile derivative **30** (120 mg, 0.45 mmol) in absolute EtOH (10 mL) was added dil. HCl (5–6 drops). After completion of the hydrolysis (ca. 12 h), the mixture was worked up according to the general procedure. The amino ester obtained was used in the next step without purification. To a soln of the crude amino ester (106 mg, 0.41 mmol) in anhyd CH_2Cl_2 (20 mL) were added DMAP (50.1 mg, 0.41 mmol) and freshly distilled Ac_2O (0.5 mL) at r.t. After completion of the reaction (24 h, TLC monitoring), the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 20% EtOAc–PE) to afford *N*-acetyl derivative **37** as a colorless liquid (48 mg, 36% over two steps).

R_f = 0.24 (30% EtOAc–PE).

IR (neat): 3436, 2925, 1738, 1649, 1265, 739 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.78 (s, 3 H, $NHCOCH_3$), 1.92–1.96 (m, 4 H, CH_2), 2.74 (s, 4 H, CH_2), 3.16 (ABq, J = 16.8 Hz, 2 H, CH_2), 3.56 (ABq, J = 16.8 Hz, 2 H, CH_2), 4.23 (q, J = 7.0 Hz, 2 H, OCH_2CH_3), 5.99 (s, 1 H, $NHCOCH_3$), 6.91 (s, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 23.2, 23.4, 29.6, 43.3, 61.7, 66.2, 125.2, 136.1, 137.2, 170.4, 173.1.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{18}H_{24}NO_3$: 302.1756; found: 302.1756.

Ethyl 2-Acetamido-1,2,3,5,6,7,8,9-octahydrocyclohepta[*f*]indene-2-carboxylate (38)

To a soln of isonitrile derivative **31** (crude reaction mixture) (78 mg, 0.27 mmol) in absolute EtOH (10 mL) was added dil. HCl (6 drops). After completion of the hydrolysis (ca. 12 h), the mixture was worked up according to the general procedure. The amino ester obtained was used in the next step without purification. To a soln of the crude amino ester (46 mg, 0.17 mmol) in anhyd CH_2Cl_2 (20 mL) were added DMAP (20 mg, 0.17 mmol) and freshly distilled Ac_2O (0.02 mL) at r.t., and the resulting mixture stirred for 12 h. After completion of the reaction, the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 40% EtOAc–PE) to afford the protected amino ester **38** as a thick liquid (30 mg, 42% over three steps).

R_f = 0.46 (20% EtOAc–PE).

IR (neat): 3439, 1735, 1654, 1265 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.0 Hz, 3 H, OCH_2CH_3), 1.60–1.63 (m, 4 H, CH_2), 1.80–1.82 (m, 2 H, CH_2), 1.92 (s, 3 H, $NHCOCH_3$), 2.75 (t, J = 5.4 Hz, 4 H, CH_2), 3.12 (ABq, J = 16.4 Hz, 2 H, CH_2), 3.57 (ABq, J = 16.4 Hz, 2 H, CH_2), 4.21 (q, J = 7.3 Hz, 2 H, OCH_2CH_3), 6.07 (s, 1 H, $NHCOCH_3$), 6.94 (s, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.2, 23.2, 28.5, 32.8, 36.7, 43.5, 61.6, 66.2, 125.3, 137.4, 142.6, 170.2, 173.0.

HRMS (Q-Tof): m/z [M + H]$^+$ calcd for $C_{19}H_{26}NO_3$: 316.1912; found: 316.1921.

Ethyl 2-Acetamido-2,3-dihydro-1*H*-cyclopenta[*a*]naphthalene-2-carboxylate (12)

To a soln of isonitrile derivative **40** (150 mg, 0.57 mmol) in absolute EtOH (10 mL) was added dil. HCl (5 drops). After completion of the hydrolysis (ca. 12 h), the mixture was worked up according to the general procedure. The amino ester obtained was used in the next step without purification. To a soln of the crude amino ester (136 mg, 0.53 mmol) in anhyd CH_2Cl_2 (20 mL) were added DMAP (65 mg, 0.53 mmol) and freshly distilled Ac_2O (0.5 mL) at r.t. After completion of the reaction (24 h, TLC monitoring), the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 20% EtOAc–PE) to afford protected amino ester derivative **12** as a colorless liquid (45 mg, 30% over two steps).

R_f = 0.32 (30% EtOAc–PE).

IR (neat): 3437, 1736, 1647, 1265, 740 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.0 Hz, 3 H, CH_2CH_3), 1.94 (s, 3 H, $NHCOCH_3$), 3.39 (dd, $J_1 = J_2$ = 16.8 Hz, 1 H, CH_a), 3.62 (dd, $J_1 = J_2$ = 17.1 Hz, 1 H, CH_b), 3.82 (dd, $J_1 = J_2$ = 16.8 Hz, 1 H, CH_a), 3.95 (dd, $J_1 = J_2$ = 17.1 Hz, 1 H, CH_b), 4.25 (q, J = 7.0 Hz, 2 H, CH_2CH_3), 6.25 (s, 1 H, $NHCOCH_3$), 7.34 (d, J = 8.6 Hz, 1 H, ArH), 7.43–7.48 (m, 2 H, ArH), 7.72 (t, J = 7.0 Hz, 2 H, ArH), 7.85 (d, J = 8.6 Hz, 1 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 23.3, 42.6, 44.9, 61.9, 65.8, 122.9, 124.1, 125.5, 126.6, 127.9, 128.7, 130.3, 132.9, 135.5, 136.9, 170.4, 173.3.

HRMS (Q-Tof): *m/z* [M + H]$^+$ calcd for $C_{18}H_{20}NO_3$: 298.1443; found: 298.1442.

Ethyl 2-Acetamido-2,3-dihydro-1*H*-cyclopenta[*l*]phenanthrene-2-carboxylate (15)

To a soln of the isonitrile derivative (crude reaction mixture) (110 mg, 0.35 mmol) in absolute EtOH (10 mL) was added dil. HCl (4–5 drops). After completion of the reaction (ca. 12 h), the mixture was worked up according to the general procedure. The amino ester obtained was used in the next step without purification. To a soln of the amino ester (100 mg, 0.32 mmol) in anhyd CH_2Cl_2 (20 mL) were added DMAP (39 mg, 0.32 mmol) and freshly distilled Ac_2O (0.03 mL) at r.t., and the resulting mixture stirred for 12 h. After completion of the reaction, the mixture was worked up according to the general procedure. The crude residue was purified by column chromatography (eluent: 30% EtOAc–PE) to afford protected amino ester **15** as a pale-yellow solid (25 mg, 30% over three steps).

Mp 194–196 °C; R_f = 0.35 (50% EtOAc–PE).

IR (KBr): 3055, 2986, 2928, 1736, 1678, 1265, 896 cm^{-1}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.3 Hz, 3 H, OCH_2CH_3), 1.94 (s, 3 H, $NHCOCH_3$), 3.70 (ABq, *J* = 16.1 Hz, 2 H, CH_2), 4.05 (ABq, *J* = 15.9 Hz, 2 H, CH_2), 4.27 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 6.23 (s, 1 H, $NHCOCH_3$), 7.63–7.65 (m, 4 H, ArH), 7.77–7.78 (m, 2 H, ArH), 8.70–8.72 (m, 2 H, ArH).

^{13}C NMR (100.6 MHz, $CDCl_3$): δ = 14.3, 23.3, 43.9, 62.0, 65.0, 123.3, 124.7, 126.3, 127.0, 129.4, 130.6, 133.8, 170.3, 173.4.

HRMS (Q-Tof): *m/z* [M + Na]$^+$ calcd for $C_{22}H_{21}NO_3Na$: 370.1419; found: 370.1418.

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