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Synthesis of novel isoindolone derivatives *via* cascade reactions. Contrasting diastereoselectivity under solution-phase *vis-a-vis* solvent-free ball-milling reaction conditions

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This manuscript is dedicated to Professor Steve Davies in celebration of his career of innovative research, and with gratitude for his service to Tetrahedron Asymmetry.

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ABSTRACT

The highly diastereoselective synthesis, crystallographic analysis, and full characterization of several novel heterocycle-fused isoindolones is described. The synthetic strategy involves a cascade Michael/aldol-like cyclization reaction between *N*-substituted phthalimides *rac*-**1** or **2** and several α,β-unsaturated electrophiles to afford the tricyclic systems pyrrolo[2,1- *a*]isoindolone and tetrahydropyrido[2,1-*a*]isoindolone. This synthetic strategy offers a convenient alternative to existing procedures for the preparation of isoindolone derivatives fused to five- and six-membered rings. X-ray crystallographic analysis allowed the determination of relative configurations and revealed that the synthesized compounds exhibit significant structural distortion, especially in the five membered rings. Relevantly, the diastereomeric distribution of products depends substantially on whether the cascade reaction is carried out under solution *vis-a-vis* solvent-free conditions.

1. Introduction

In recent years, isoindolin-1-one derivatives have received significant attention from synthetic organic chemists because natural alkaloids such as (±)-chilenine [1], (±)-lennoxamine (±)-nuevamine [2], (±)-palmanine [3], and magallanesine [4] contain this nitrogenated heterocyclic nucleus (Fig. 1). In this regard, several research groups have been inspired by the structures of the above natural products to develop innovative synthetic routes for their preparation [5,6].

In particular, fused isoindolones such as the tricyclic systems pyrrolo[2,1-*a*]isoindolone and tetrahydropyrido[2,1-*a*]isoindolone constitute an attractive synthetic target due to the significant challenge of constructing heterofused rings with multiple functional groups. Salient methods for the synthesis of these tricyclic systems include cyclization reactions [7], photochemical reactions [8], cycloaddition reactions [9], Horner-Wadsworth-Emmons reactions [10], condensation reactions [11], coupling reactions [12], Pictet-Spengler reactions [13], and multicomponent cascade reactions [14]. Biologically active compounds containing these tricyclic scaffolds include cyclin-dependent kinase 4 (Cdk4) inhibitors [15], topoisomerase II inhibitors [16], cyclin-dependent kinase 5 (Cdk5) and glycogen synthase kinase 3 (GSK3) dual inhibitors [17], and urotensin-II receptor antagonists [18] (Fig. 2).

In this regard, several years ago one of our groups reported a novel synthetic strategy to access pyrrolo[2,1-*a*]isoindolones based

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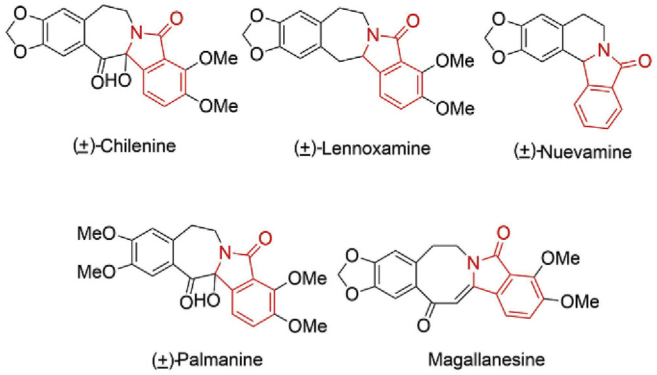


Fig. 1. Natural alkaloids containing the isoindolin-1-one skeleton.

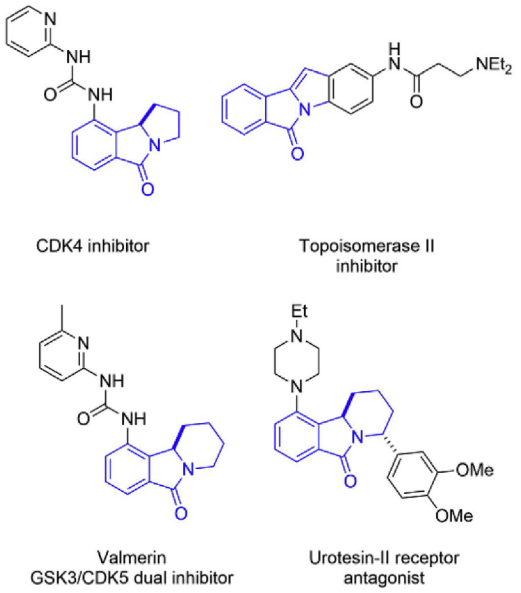


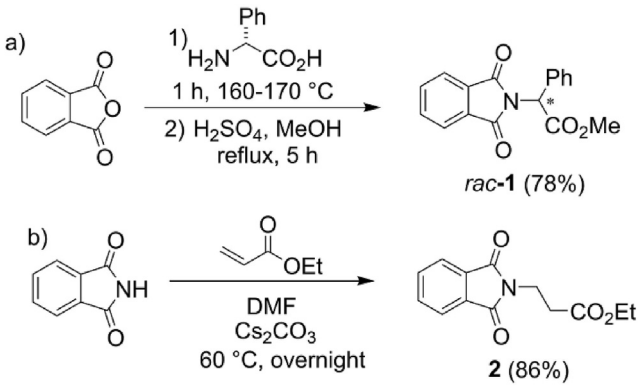
Fig. 2. Examples of biologically active compounds containing the pyrrolo[2,1-*a*]isoindolone and tetrahydropyrido[2,1-*a*]isoindolone core.

on a cascade process involving the Michael addition reaction of *N*-substituted phthalimides to α,β-unsaturated esters followed by an aldol-like cyclization reaction [19]. Herein, we wish to report remarkable findings regarding the role of functional groups present in the six-membered rings on the diastereoselectivity of the cascade reactions of interest. Furthermore, we discuss the characterization process and present the development of simple methodologies for the synthesis of several novel tricyclic compounds that contain the pyrrolo[2,1-*a*]isoindolone and tetrahydropyrido[2,1-*a*]isoindolone scaffolds, both under solution phase and under solvent-free ball-milling reaction conditions.

2. Results and discussion

2.1. Synthesis and characterization of compounds rac-3a-b, rac-4a-d, rac-5, rac-6a-c, and rac-7

Phthalimide *rac*-**1** was synthesized in 78% yield from phthalic anhydride and (*R*)-phenylglycine followed by Fisher's esterification (Scheme 1a). We obtained racemic phthalimide **1** due to racemization of (*R*)-phenylglycine during the high-temperature reaction [19c] (racemization confirmed by chiral HPLC). On the other hand, phthalimide **2** was prepared in 86% yield through a Michael

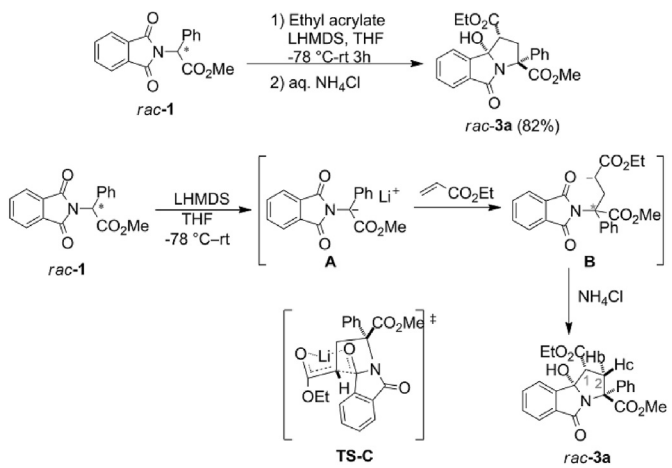


Scheme 1. Synthesis of *N*-substituted phthalimides *rac*-**1** and **2**.

reaction between the parent phthalimide and ethyl acrylate (Scheme 1b).

With phthalimides *rac*-**1** and **2** in hand, we carried out a cascade Michael/aldol-like cyclization reaction to obtain the corresponding tricyclic system *rac*-**3a** that incorporates the required isoindolone skeleton. Based on our previously reported method [19] the cascade reaction between phthalimide *rac*-**1** and ethyl acrylate was carried out in the presence of lithium bis(trimethylsilyl)amide (LHMDS) at low temperature to give tricycle *rac*-**3a** in 82% yield as a *single diastereoisomer* in racemic form, as confirmed by chiral HPLC (Scheme 2) [19a]. The cascade process takes place by conjugate addition of (achiral) carbanion **A** to ethyl acrylate to form the (racemic) anionic intermediate **B**, that adds diastereoselectively in an intramolecular fashion to one of the diastereotopic carbonyl groups of the phthalimide moiety to form the new carbon-carbon bond. The relative stereochemistry observed in the tricycle *rac*-**3a** can be explained by a Zimmerman-Traxler type transition state **TS-C**, as shown in Scheme 2. In this process, two bonds and three stereogenic centers are formed in a single step with high diastereoselectivity.

The relative configuration of heterocyclic compound *rac*-**3a** was determined by ^{1}H NMR and X-ray diffraction analysis. In particular, the ^{1}H NMR spectrum of *rac*-**3a** shows a doublet of doublets at 3.27 ppm with geminal and vicinal coupling constants $^2J = 13.0$ Hz and $^3J = 7.2$ Hz, respectively, that was assigned to H(2c), a triplet at 3.41 ppm with $^3J = 12.7$ Hz that was assigned to H(2b), and a doublet of doublets at 3.58 ppm with $^3J = 7.2$ Hz and $^3J = 12.4$ Hz



Scheme 2. Cascade Michael/aldol-like cyclization reaction and the proposed transition state.

that was assigned to H(1). These coupling constants are consistent with those reported for pyrrolo[2,1-*a*]isoindolone, whose relative configuration is known [19]. On the order hand, an X-ray diffraction structure of suitable crystals of *rac*-**3a** (Fig. 3) [20] confirmed the assignment of the relative configuration based on analysis of the ^{1}H NMR spectra.

When the cascade reaction was carried out with acrylonitrile as the electrophile under the same reaction conditions employed for the preparation of *rac*-**3a**, three products were observed by thin layer chromatography (TLC). Following purification by column chromatography, the less polar compound *rac*-**4a** was obtained in 84% yield, whereas the more polar compounds *rac*-**4b** and *rac*-**4c** were isolated in 4.7% and 2.5% yields, respectively (Scheme 3).

The relative configuration of *rac*-**4a** was tentatively established by comparison with the NMR data of a similar compound [19]. Finally, the assignment of the relative configuration at C(1) in *rac*-**4c** was established by NMR spectroscopic analysis. In particular, the ^{1}H NMR spectrum of *rac*-**4c** showed a doublet of doublets at 3.02 ppm with vicinal and geminal coupling constants $^{3}J = 0.92$ Hz and $^{2}J = 14.4$ Hz, respectively, that was assigned to H(2b), whereas H(2c) appears at 4.07 ppm as a doublet of doublets with $^{3}J = 8.5$ Hz, and $^{2}J = 14.4$ Hz. H(1) appears at 3.97 ppm as a doublet with $^{3}J = 8.5$ Hz, which suggests a dihedral angle near 20° between H(1) and H(2b), and for H(1) with H(2c) near 100°. The relative configuration of the three stereogenic centers was confirmed by single-crystal X-ray diffraction analysis [21], and it can be observed that the A and B rings are located in the same plane, while the C ring forms an angle of 120° with respect to the plane. Interestingly, the structures *rac*-**4c** and *rac*-**4d** present differences in their conformational arrangement as consequence of the different configuration (Cf. Fig. 4 and Fig. 6).

In the case of *rac*-**4b**, its relative configuration was established by comparison with the chemical shifts and coupling constants recorded for diastereoisomer *rac*-**4c** (Table 1).

Previously, we reported that the cascade reaction of interest is stereoselective when Michael acceptors such as diethyl maleate are employed in the reaction [19]. We now report that when phthalimide *rac*-**1** is treated with diethyl maleate under the same reaction conditions, tricycle *rac*-**5** was obtained in 62% yield as a single racemic stereoisomer (Scheme 4). ^{1}H NMR spectroscopic analysis gives evidence of the *cis* relative configuration of the hydrogens H(1) and H(2) with $^{3}J = 11.6$ Hz [19].

With the aim to further explore the scope of this cascade reaction, it was decided to synthesize tetrahydropyrido[2,1-*a*]isoindolone. This was achieved by reacting phthalimide **2** and ethyl acrylate under the established solution reaction conditions,

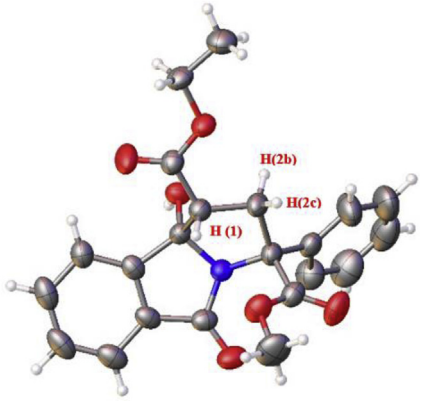
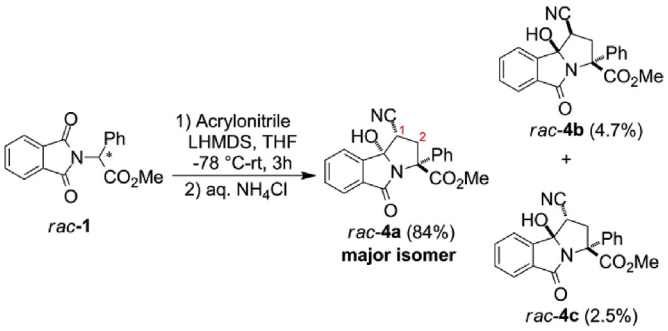


Fig. 3. X-ray crystallographic structure of *rac*-**3a** showing the relative configuration of the three-stereogenic centers [20].



Scheme 3. Synthesis of pyrrolo-isoindolone *via* a cascade reaction.

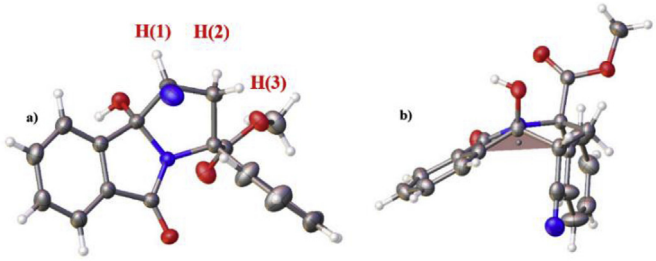


Fig. 4. a) X-ray crystallographic structure of *rac*-**4c** showing the relative configuration of the three stereogenic centers. b) Side view [21].

observing by TLC three products after 4 h. Following workup and purification by column chromatography, the less polar compound *rac*-**6a** was obtained in 44% yield, whereas the remaining products were identified as a mixture of diastereoisomers (Scheme 5a). In contrast, when phthalimide **2** was treated with diethyl fumarate employing the same reactions conditions, product *rac*-**7** was obtained in 66% yield as a single racemic stereoisomer (Scheme 5b). The relative configuration between C(1) and C(3) in tricyclic derivative *rac*-**6a** and *rac*-**7** was determined based on their ^{1}H NMR *J*-coupling patterns. Selected ^{1}H and ^{13}C NMR chemical shifts and coupling constants are collected in Table 2.

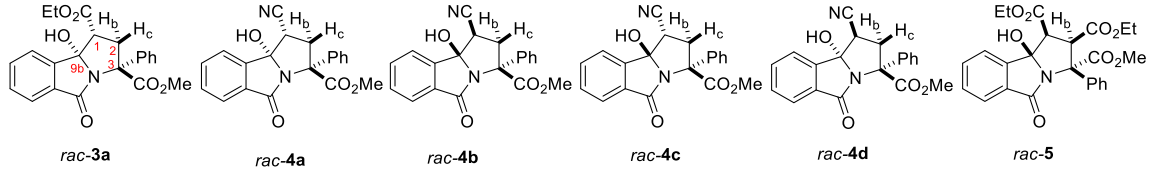
Furthermore, the relative configuration of *rac*-**6a** and *rac*-**7** was unambiguously assigned by single-crystal X-ray diffraction analysis [22,23] (see Scheme 5 and Fig. 5). In the crystal structure, the piperidine ring adopts a chair conformation with the ester groups in the equatorial orientation.

In our research group we have significant interest in the development of solvent-free organic reactions [24]. In this regard, we turned our attention towards mechanochemical activation provided by high-speed ball-milling technique (HSBM) [25] to promote the cascade reactions of interest. In this regard, several research groups have reported cascade reactions that were carried out under HSBM conditions [26].

To examine the feasibility of a solvent-free mechanochemical version of the cascade Michael/aldol-like cyclization reaction of interest, phthalimide *rac*-**1**, ethyl acrylate, and Cs_2CO_3 as an inorganic base were milled under ball mill conditions. After 90 min of milling, TLC revealed various spots which were identified as the target compound *rac*-**3a** (16%), the Michael adduct *rac*-**3b** (35%) and other minor side-products that were not characterized (Scheme 6a). Interestingly, the main diastereoisomeric product *rac*-**3a** was not observed in the solution-phase experiment (Scheme 6a).

When the cascade reaction was performed with acrylonitrile instead of ethyl acrylate under ball-milling conditions, TLC revealed the formation of three products. Diastereoisomer *rac*-**4a** was obtained in 30% yield together with recovered starting material *rac*-**1**

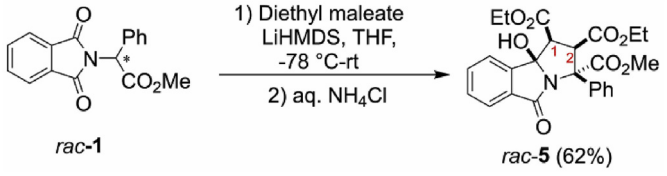
Table 1
Selected ^{1}H and ^{13}C NMR chemical shifts (ppm) and *J* coupling constants (Hz) for the tricyclic compounds *rac*-**3a**, *rac*-**4a**-d, and *rac*-**5**.



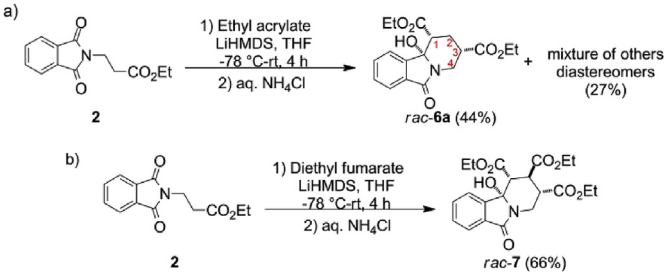
rac-**3a** *rac*-**4a** *rac*-**4b** *rac*-**4c** *rac*-**4d** *rac*-**5**

Compound	*rac*-**3a**[a]	*rac*-**4a**[a]	*rac*-**4a**[b]	*rac*-**4b**[b]	*rac*-**4c**[b]	*rac*-**4d**[b]	*rac*-**5**[a]
δ (H-1/C-1)	3.58/49.2	3.55/36.2	3.64/37.2	3.99/38.3	3.97/37.8	3.99/38.3	3.79/52.7
δ (H-2b/C-2)	3.41/44.6	3.45/45.6	3.32/46.7	3.47/47.4	3.02/48.3	3.47/47.4	4.76/60.9
δ (H-2c/C-2)	3.27/44.6	3.40/45.6	3.67/46.7	3.62/47.4	4.07/48.3	3.62/47.4	–
J (H-1/H-2b)	12.4	11.1	10.7	7.9	0.92	7.8	11.6
J (H-1/H2c)	7.2	7.6	6.7	0.74	8.5	[c]	–
J (H-2b/H-2c)	13.0	12.1	11.0	14.0	14.4	13.9	–
δ (C-3)	68.5	69.0	69.5	69.3	69.7	69.3	70.5
δ (C-9b)	95.8	95.0	96.0	99.3	98.8	99.3	94.5
δ (CN)	–	116.2	117.6	118.4	119.9	118.4	–

[a] Spectra were determined in $CDCl_3$.
[b] Spectra were determined in acetone-d_6.
[c] Not resolved.



Scheme 4. Stereoselective cascade reaction providing *rac*-**5**.



Scheme 5. Synthesis of tetrahydropyrido[2,1-*a*]isoindolone, *rac*-**6a** and *rac*-**7** *via* a cascade reaction.

(30% yield). In addition, compound *rac*-**4b** (24% yield) and novel isomer *rac*-**4d** (6% yield) were isolated by fractional crystallization. Interestingly, product *rac*-**4d** was only formed under HSBM conditions (Scheme 6b). Although yields and the stereoselectivity are lower in comparation with solution-phase assays, the exclusive formation of certain diastereomers under HSBM conditions is worthy of mention.

The molecular structure and relative configuration of diastereoisomer *rac*-**4d** was established by NMR and single-crystal X-ray diffraction analysis [27] (Table 2 and Fig. 6). As was observed in the X-ray crystallographic structures corresponding to compounds *rac*-**3a** and *rac*-**4c**, the pyrrolidine ring in tricycle *rac*-**4d** adopts an envelope conformation. This finding is interesting because it shows that structures *rac*-**4c** and *rac*-**4d** present substantial differences in conformational arrangement as a result of the corresponding diastereomeric configurations (Cf. Figs. 4 and 6).

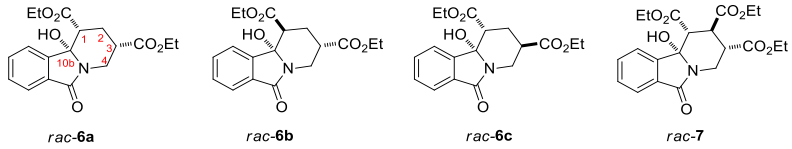
Based on these results, it was decided to carry out the preparation of tetrahydropyrido-isoindolones under ball milling conditions. An initial experiment consisted of *N*-alkylation of phthalimide with ethyl acrylate in the presence of 1,8-diazabicyclo [5.4.0]undec-7-ene (DBU) under solvent-free ball-milling conditions. This procedure afforded the desired phthalimide **2** in 70% yield. To achieve the desired one-pot sequential mechanochemical reaction [28], phthalimide was treated with ethyl acrylate (4 equiv.) in the presence of DBU (1.1 equiv.) and ball-milled for an additional 90 min, giving rise to product **2** in essentially quantitative yield. At this point, NaH was added to the milling jar and the reaction mixture was milled for an additional 90 min. TLC analysis showed three spots, that were separated by flash chromatography to afford tetrahydropyrido-isoindolone *rac*-**6a** in 32% yield. In addition, tricyclic compounds *rac*-**6b** and *rac*-**6c** were isolated (30% combined yield) and fully characterized (Scheme 7).

The relative configuration between C(1) and C(3) in tricyclic derivatives *rac*-**6b** and *rac*-**6c** was initially assigned by analysis of *J*-coupling patterns in the ^{1}H NMR spectra (Table 2). These assignments were confirmed by X-ray crystallographic analysis of these heterocycles, isolated from the ball milling experiments [29,30]. As can be appreciated from Fig. 7, in both *rac*-**6b** and *rac*-**6c** the piperidine ring adopts a chair conformation, where the ester groups adopt axial and equatorial orientations.

It is worth noting that the mechanochemical activation [31] achieved by ball milling has allowed the isolation and characterization of diastereomeric compounds such as *rac*-**4d**, *rac*-**6b**, *rac*-**6c**, and elusive intermediate *rac*-**3b**, that are not observed in solution-phase experiments [31].

In conclusion, several novel tricyclic nitrogenated heterocycles were synthesized *via* a cascade Michael/aldol-like cyclization reaction both under solution-phase and solvent-free ball milling conditions, thus allowing to build up molecular complexity with high efficiency. Most importantly, this cascade process is a powerful synthetic tool for the construction of fused isoindolones such as the pyrrolo[2,1-*a*]isoindolone and tetrahydropyrido[2,1-*a*]isoindolone scaffolds in a one-pot process. Research on further applications and expansion of this cascade process are underway in our laboratories. Relevantly, the diastereomeric distribution of products depends substantially on whether the cascade reaction is carried out under solution *vis-a-vis* solvent-free ball milling conditions.

Table 2
Selected ^{1}H and ^{13}C NMR chemical shifts (ppm) and *J* coupling constants (Hz) for the tricyclic compounds *rac*-**6a**-**c**, and *rac*-**7**.



rac-**6a** *rac*-**6b** *rac*-**6c** *rac*-**7**

Compound[a]	*rac*-**6a**	*rac*-**6b**	*rac*-**6c**	*rac*-**7**
δ (H-1)	[b]	3.39	2.92	2.56
δ (H-4_{ax})	3.27	3.09	3.42	3.23
δ (H-4_{eq})	4.51	4.18	4.67	4.47
J (H-4_{ax}/H-3)	12.6	12.5	4.6	12.3
J (H-4_{eq}/H-3)	4.8	5.1	1.6	5.2
J (H-1/H-2_{eq})	[c]	2.2	4.3	–
J (H-1/H-2_{ax})	[c]	4.9	12.6	12.1
δ (C-4)	36.5	36.5	36.3	35.7
δ (C-10b)	84.8	85.2	85.0	84.8

[a] Spectra were determined in $CDCl_3$.
[b] Overlapped signal.
[c] Not resolved.

3. General information

Unless otherwise indicated, all reagents were purchased from Sigma-Aldrich and used without further purification. The progress of reactions was routinely monitored by TLC on silica gel 60 (precoated F254 Merck plates) under UV lamp (254 nm) irradiation to visualize starting materials and products. Flash chromatography was performed using silica gel (230–400 mesh).

Melting points were measured on a Melt-Temp "Electrothermal" apparatus and are uncorrected. NMR spectra were recorded in Bruker 400 Avance III HD (400 MHz) and JEOL ECA (500 MHz) spectrometers. Signal multiplicity was abbreviated as follows: s = singlet, br s = broad singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, quint = quintet, sext = sextet, hept = septet, m = multiplet. Infrared spectra were recorded on a Perkin-Elmer (PC16, Spectrum GX) FT-IR spectrometer with attenuated total reflectance (ATR).

HRMS were recorded on an LC/MSD-TOF1069A Agilent mass spectrometer. The HPLC analysis were acquired in a Dionex HPLC Ultimate 3000 with a UV/Visible detector, with diode array. The structural X-ray crystallographic data were obtained on a Bruker D8 Venture diffractometer. Mechanochemical experiments were carried out in a Retsch MM200 ball mill that was equipped with stainless steel jars (internal diameter: 2 cm; internal length: 4.2 cm; external diameter: 3 cm; external length: 6.5 cm) and stainless-steel balls (diameter: 11 mm).

3.1. Synthesis, crystallization and spectroscopic data

3.1.1. Methyl 2-(1,3-dioxoisoindolin-2-yl)-2-phenylacetate, (rac-*1*)

A round-bottom flask (500 mL) containing a magnetic stirrer and equipped with a reflux condenser was charged with phthalic anhydride (9.28 g, 62.65 mmol) and D-(−)-α-phenylglycine (10 g, 66.15 mmol). The resulting mixture was heated to 180–190 °C for 1 h and then allowed to cool down to room temperature, before the addition of MeOH (150 mL) and sulfuric acid (2 mL) [19c]. The reaction mixture was heated to reflux for 5 h, then was added potassium carbonate (4.95 g) and then the solvent was evaporated under vacuum. The residue was dissolved in water (200 mL) and EtOAc (100 mL), and the aqueous layer was extracted with EtOAc (3 × 30 mL). The combined organic layers were washed with brine (30 mL), dried over anhydr. Na_2SO_4 and concentrated under vacuum. The crude product was purified by column chromatography (hexane/EtOAc 9:1 v/v) to afford 14.5 g (78.0% yield) of *rac*-**1** as a colorless solid, mp 99.6–100.5 °C (literature mp 116–117 °C) [32], $R_f = 0.4$ (hexane/EtOAc 7:3 v/v). HPLC separation conditions: column AD-H, 90:10 Hexane-IPA, Flux 1.0 mL/min, retention time: 17.8 and 24.1 min (see ESI). ^{1}H NMR (400 MHz, $CDCl_3$) 3.81 (3H, s, OCH_3), 6.02 (1H, s, CH), 7.30–7.38 (3H, m, H_{ar}), 7.53–7.56 (2H, m, H_{ar}), 7.69–7.73 (2H, m, H_{ar}), 7.82–7.86 (2H, m, H_{ar}). ^{13}C NMR (100.5 MHz, $CDCl_3$) 53.0 (OCH_3), 55.8 (CH), 123.6 (2 × CH_{ar}), 128.5 (2 × CH_{ar}), 128.6 (CH_{ar}), 129.7 (2 × CH_{ar}), 131.8 (2 × C_{ipso}), 134.2 (2 × CH_{ar}), 134.4 (C_{ipso}), 167.0 (2 × NC=O), 168.5 (OC=O).

3.1.2. Ethyl 3-(1,3-dioxoisoindolin-2-yl)propanoate, (*2*)

In a 100 mL round-bottomed flask containing a magnetic stirrer, phthalimide (2.0 g, 13.59 mmol) was dissolved in dry DMF (30 mL) before the addition of Cs_2CO_3 (5.31 g, 16.31 mmol) and the reaction mixture was stirred for a few minutes. Subsequently, ethyl acrylate (1.8 mL, 16.56 mmol) was added and then the resulting reaction mixture was heated to 60 °C overnight. The solvent was evaporated under vacuum and the residue was extracted with water (50 mL) and EtOAc (3 × 50 mL). The combined organic layers were washed with aq. $NaHCO_3$ (50 mL) and brine (50 mL) and dried over anhydr. Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography (hexane/EtOAc 7:3 v/v) to afford 2.9 g (86% yield) of **2** as a crystalline solid, mp 61–62 °C, (literature mp 64–65 °C [33]. $R_f = 0.24$ (hexane/EtOAc 8:2 v/v). ^{1}H NMR (400 MHz, $CDCl_3$) 1.22 (3H, t, $J = 7.2$ Hz, CH_3), 2.72 (2H, t, $J = 7.2$ Hz, CH_2), 4.00 (2H, t, $J = 7.2$ Hz, CH_2), 4.13 (2H, q, $J = 7.2$ Hz, OCH_2), 7.70–7.74 (2H, m, H_{ar}), 7.83–7.87 (2H, m, H_{ar}). ^{13}C NMR (100.5 MHz, $CDCl_3$) 14.1 (CH_3), 33.0 (CH_2), 33.8 (CH_2), 60.8 (OCH_2), 123.3 (2 × CH_{ar}), 132.0 (2 × C_{ipso}), 134.0 (2 × CH_{ar}), 168.0 (2 × NC=O), 170.8 (OC=O). HRMS (ESI-TOF): MH^+, found: 248.0924. calcd. $C_{13}H_{13}NO_4 + H^+$: 248.0917.

3.2. Preparation of compounds rac-*3a*, rac-*4a-c*, rac-*5*, rac-*6a* and rac-*7* under solution conditions

3.2.1. 1-Ethyl 3-methyl (1S,3S,9bR)- and (1R,3R,9bS)-9b-hydroxy-5-oxo-3-phenyl-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindole-1,3-dicarboxylate, (rac-*3a*)

A solution of *rac*-**1** (0.5 g, 1.69 mmol) and ethyl acrylate (0.2 mL, 1.86 mmol) in dry THF (20 mL) was cooled to −78 °C under nitrogen

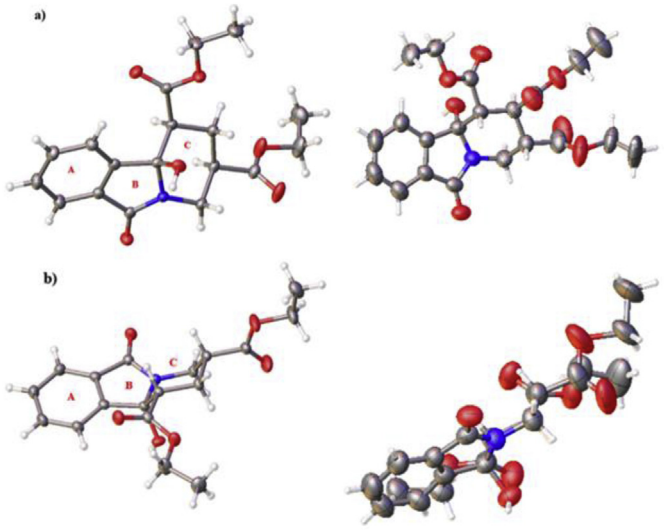
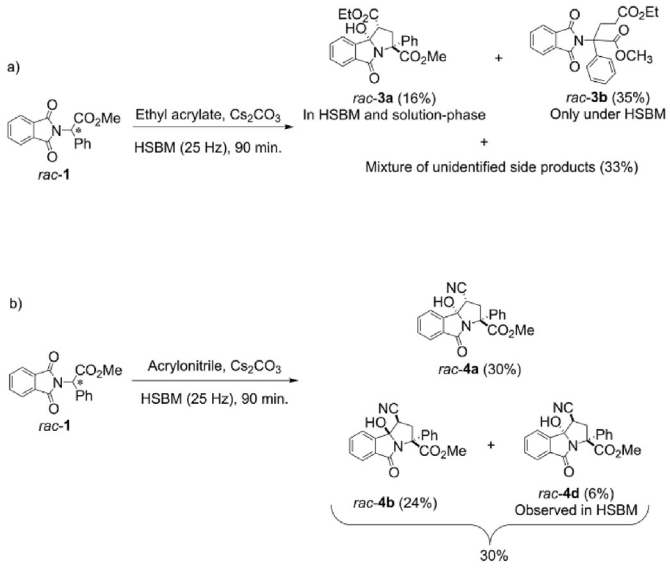


Fig. 5. a) Crystallographic structures for *rac*-**6a** and *rac*-**7**, showing the relative configuration of the stereogenic centers. b) Chair conformation for *rac*-**6a** and *rac*-**7** [22,23].



Scheme 6. Cascade reactions under solvent-free ball-milling conditions for the synthesis of several pyrrolo-isoindolones. a) Formation of *rac*-**3b** took place under ball-milling conditions. b) A novel diastereomeric product *rac*-**4d** formed under ball-milling conditions.

atmosphere. Subsequently, lithium bis(trimethylsilyl)amide (1 M solution in THF, LHMDS, 1.9 mL, 1.9 mmol) was added dropwise and the reaction mixture was stirred for 3 h at −78 °C. The resulting mixture was warmed to room temperature for 2 h before the addition of aq. NH_4Cl (10 mL), and the reaction mixture was extracted with EtOAc (3 × 20 mL). The organic extracts were combined and washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL) and dried over anhydr. Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography (hexane/EtOAc 8:2 v/v) to afford 545 mg (82% yield) of *rac*-**3a** as a crystalline solid, mp 164–166 °C, $R_f = 0.2$ (hexane/EtOAc 8:2 v/v). HPLC separation conditions: column AS-H, 90:10 Hexane-IPA, Flow 1.5 mL/min, retention time: 17.3 and 38.8 min (see ESI). ^{1}H NMR (400 MHz, $CDCl_3$) 1.38 (3H, t, $J = 7.1$ Hz, CH_3), 3.27 (1H, dd, $J = 7.1$, 13.0 Hz, C*H*H diastereotopic proton), 3.43 (2H, t, $J = 12.7$ Hz, CH, OH), 3.57 (1H, dd, $J = 7.2$, 12.3 Hz, CH*H* diastereotopic proton), 3.64 (3H, s, OCH_3), 4.24–4.36 (2H, m, OCH_2), 7.28–7.37 (3H, m, H_{ar}), 7.49–7.56 (3H, m, H_{ar}), 7.64 (1H, t, $J = 7.4$ Hz, H_{ar}), 7.78 (1H, d, $J = 7.5$ Hz, H_{ar}), 7.84 (1H, d, $J = 7.6$ Hz, H_{ar}). ^{13}C NMR (100.5 MHz, $CDCl_3$) 14.2 (CH_3), 44.5 (CH_2), 49.2 (CH), 53.1 (OCH_3), 61.6 (OCH_2), 68.5 (C), 95.8 (C–OH), 123.8 (CH_{ar}), 124.1 (CH_{ar}), 127.1 (2 × CH_{ar}), 127.6 (CH_{ar}), 128.00 (2 × CH_{ar}), 130.3 (CH_{ar}), 131.6 (C_{ipso}), 133.3 (CH_{ar}), 140.7 (C_{ipso}), 145.6 (C_{ipso}), 169.1 (NC═O), 169.9 (EtOC = O), 172.0 (MeOC = O). FT-IR/ATR ν cm^{-1}: 3442, 3269, 2984, 1743, 1706, 1395, 1318, 1259, 1168, 1129, 1091, 1002, 877, 763, 696, 565, 503. HRMS (ESI-TOF): *m*/*z* calculated for $C_{22}H_{21}NO_6 + H^+$: 396.1442; [M + H$^+$]; found: 396.1434.

3.2.2. *Methyl (1R,3S,9bR)- and (1S,3R,9bS)-1-cyano-9b-hydroxy-5-oxo-3-phenyl-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindole-3-carboxylate, (rac-**4a**)*

The procedure described above for the preparation of *rac*-**3a** was followed with *rac*-**1** (0.5 g, 1.69 mmol), acrylonitrile (0.12 mL, 1.86 mmol), and LHMDS (1 M solution, 1.9 mL, 1.9 mmol). TLC (CH_2Cl_2/hexane 9:1, eluted three times) of the reaction crude showed three components with $R_f = 0.42$, 0.25, and 0.21, which were separated by column chromatography (CH_2Cl_2/hexane 9:1 v/v). The fraction with $R_f = 0.42$ afforded 495 mg (84% yield) of *rac*-**4a** as a colorless solid with mp 242–244 °C (dec.). ^{1}H NMR (400 MHz, Acetone-d_6) 3.32 (1H, t, $J = 11.0$ Hz, CH), 3.60 (3H, s, OCH_3), 3.63 (1H, ddd, $J = 1.9$, 6.7 Hz C*H*H diastereotopic proton), 3.67 (1H, dd, $J = 6.7$, 11.0 Hz, CH*H* diastereotopic proton), 6.42 (1H, d, $J = 1.8$ Hz, OH), 7.31–7.43 (3H, m, H_{ar}), 7.55–7.60 (2H, dt, $J = 1.5$, 6.8, H_{ar}), 7.68–7.73 (1H, m, H_{ar}), 7.74–7.85 (3H, m, H_{ar}). ^{13}C NMR (100.5 MHz, Acetone-d_6) 37.2 (CH), 46.7 (CH_2), 53.2 (OCH_3), 69.5 (C_q), 96.0 (C–OH), 117.6 (CN), 123.6 (2 × CH_{ar}), 124.6 (2 × CH_{ar}), 128.2 (2 × CH_{ar}), 128.3 (CH_{ar}), 128.5 (2 × CH_{ar}), 131.6 (2 × CH_{ar}), 132.6 (C_{ipso}), 134.5 (2 × CH_{ar}), 141.9 (C_{ipso}), 146.1 (C_{ipso}), 169.1 (NC═O), 171.8 (OC═O). FT-IR/ATR ν cm^{-1}: 3333, 2962, 1759, 1701, 1691, 1614, 1467, 1447, 1355, 1160, 1088, 1025, 1002, 877, 754, 693, 650, 566. HRMS (ESI-TOF): *m*/*z* calculated for $C_{20}H_{16}N_2O_4 + H^+$: 349.1183; [M + H$^+$]; found: 349.1182.

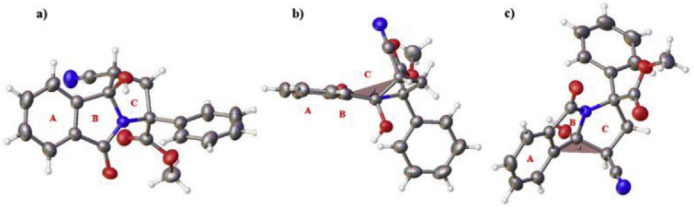
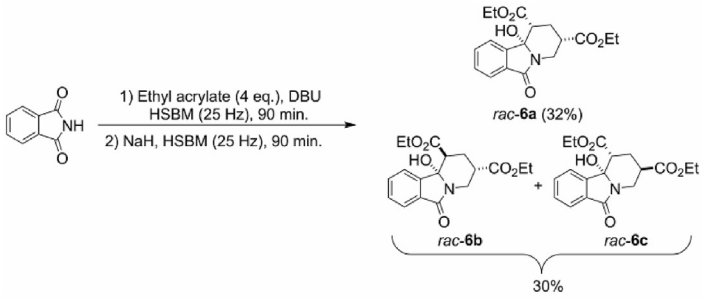


Fig. 6. a) X-ray crystallographic structure of *rac*-**4d** showing the relative configuration of the stereogenic centers. b) Side view of *rac*-**4c**. c) Front view of *rac*-**4d** [27].



Scheme 7. Cascade reaction under solvent-free ball-milling conditions for the preparation of tetrahydropyrido-isoindolones *rac*-**6a-c**.

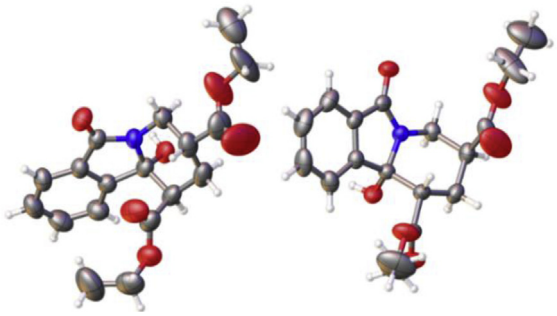


Fig. 7. Crystallographic structures for *rac*-**6c** (right) and *rac*-**6b** (left) showing the relative configuration of the stereogenic centers [29,30].

3.2.3. Methyl (1R,3R,9bR)- and (1S,3S,9bS)-1-cyano-9b-hydroxy-5-oxo-3-phenyl-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindole-3-carboxylate, (rac-**4b**)

The fraction with $R_f = 0.25$ (see above) was isolated to give 28 mg (4.7% yield) of *rac*-**4b** as a colorless solid with mp 120–122 °C (dec.). ^{1}H NMR (400 MHz, Acetone-d_6) 3.49 (1H, dd, $J = 7.3$, 14.2 Hz, C*H*H diastereotopic proton), 3.61 (3H, s, OCH_3), 3.64 (1H, dd, $J = 0.92$, 14.0 Hz, CH*H* diastereotopic proton), 4.01 (1H, dd, $J = 3.0$, 7.9 Hz, CH), 6.00 (1H, br s, OH), 7.27–7.40 (3H, m, H_{ar}), 7.50–7.54 (2H, m, H_{ar}), 7.65–7.69 (1H, m, H_{ar}), 7.74–7.82 (3H, m, H_{ar}). ^{13}C NMR (100.5 MHz, Acetone-d_6) 38.3 (CH), 47.4 (CH_2), 52.4 (OCH_3), 69.3 (C_q), 99.3 (C–OH), 118.4 (CN), 124.26 (CH), 124.33 (CH_{ar}), 128.15 (2 × CH_{ar}), 128.17 (CH_{ar}), 128.4 (2 × CH_{ar}), 131.4 (CH_{ar}), 133.4 (C_{ipso}), 134.2 (CH_{ar}), 142.9 (C_{ipso}), 145.5 (C_{ipso}), 167.8 (NC=O), 171.1 (OC=O). HRMS (ESI-TOF): *m/z* calculated for $C_{20}H_{16}N_2O_4$ + H: 349.1183; $[M + H]^+$; found: 349.1186.

3.2.4. Methyl (1S,3R,9bR)- and (1R,3S,9bS)-1-cyano-9b-hydroxy-5-oxo-3-phenyl-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindole-3-carboxylate, (rac-**4c**)

The fraction with $R_f = 0.21$ (see above) was isolated to give 15 mg (2.5% yield) of *rac*-**4c** as a colorless solid with mp 190–193 °C (dec.). ^{1}H NMR (400 MHz, Acetone-d_6) 3.02 (1H, dd, $J = 5.11$, 14.4 Hz, CH), 3.85 (3H, s, OCH_3), 3.97 (1H, d, $J = 8.5$ Hz, C*H*H diastereotopic proton), 4.07 (1H, dd, $J = 7.64$, 14.4 Hz, C*H*H diastereotopic proton), 6.13 (1H, br s, OH), 7.30–7.38 (5H, m, H_{ar}), 7.61–7.63 (2H, m, H_{ar}), 7.69–7.76 (1H, m, H_{ar}), 7.78–7.80 (1H, m, H_{ar}). ^{13}C NMR (100.5 MHz, Acetone-d_6): δ (ppm) 37.8 (CH), 48.3 (CH_2), 53.2 (OCH_3), 69.7 (C_q), 98.8 (C–OH), 119.9 (CN), 123.9 (CH_{ar}), 124.1 (CH_{ar}), 128.0 (2 × CH_{ar}), 128.8 (CH_{ar}), 129.1 (2 × CH_{ar}), 131.4 (CH_{ar}), 133.7 (CH_{ar}), 134.9 (C_{ipso}), 137.9 (C_{ipso}), 143.3 (C_{ipso}), 163.0 (NC=O), 173.9 (OC=O). HRMS (ESI-TOF): *m/z* calculated for $C_{20}H_{16}N_2O_4$ + H: 349.1183; $[M + H^+]$; found: 349.1179.

3.2.5. 1,2-Diethyl 3-methyl-icarboxylate, (rac-***5***)

The procedure described above was followed with *rac*-**1** (0.5 g, 1.69 mmol), diethyl maleate (0.30 mL, 1.86 mmol), and LiHMDS solution 1 M (1.9 mL, 1.9 mmol). The crude product was purified by column chromatography (hexane/EtOAc 7:3 v/v) to afford 489 mg (62% yield) of *rac*-**5** as a colorless oil that solidified on storage, mp 146–150 °C, $R_f = 0.3$ (hexane/EtOAc 6:4 v/v). ^{1}H NMR (500 MHz, $CDCl_3$) 1.26 (3H, t, $J = 7.1$ Hz, CH_3), 1.37 (3H, t, $J = 7.1$ Hz, CH_3), 3.17 (1H, br s, OH), 3.61 (3H, s, OCH_3), 3.79 (1H, d, $J = 11.6$ Hz, CH), 4.16–4.25 (2H, m, OCH_2), 4.29–4.74 (2H, m, OCH_2), 4.76 (1H, d, $J = 11.6$ Hz, CH), 7.31–7.39 (3H, m, H_{ar}), 7.54–7.57 (1H, m, H_{ar}), 7.63–7.66 (1H, m, H_{ar}), 7.76–7.81 (4H, m, H_{ar}). ^{13}C NMR (125.7 MHz, $CDCl_3$) 13.9 (CH_3), 14.2 (CH_3), 52.7 (CH), 53.0 (OCH_3), 60.9 (CH), 61.7 (OCH_2), 62.0 (OCH_2), 70.5 (C), 94.5 (C–OH), 123.8 (CH_{ar}), 124.2 (CH_{ar}), 127.5 (2 × CH_{ar}), 127.9 (CH_{ar}), 128.0 (2 × CH_{ar}), 130.6 (CH_{ar}), 131.2 (C_{ipso}), 133.3 (CH_{ar}), 140.3 (C_{ipso}), 144.9 (C_{ipso}), 167.7 (NC=O), 168.5 (OC=O), 169.7 (OC=O), 169.9 (OC=O). FT-IR/ATR ν cm^{-1}: 3435, 3391, 2984, 1769, 1730, 1710, 1699, 1468, 1373, 1267, 1125, 1096, 1005, 870, 773, 697, 585. HRMS (ESI-TOF): *m/z* calculated for $C_{25}H_{25}NO_8 + H^+$: 468.1653; $[M + H^+]$; found: 468.1653.

3.2.6. Diethyl (1R,3S,10bS)- and (1S,3R,10bR)-10b-hydroxy-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindole-1,3-dicarboxylate, (rac-***6a***)

A solution of **2** (300 mg, 1.21 mmol) and ethyl acrylate (0.2 mL, 1.84 mmol) in dry THF (25 mL) was cooled to −78 °C under nitrogen atmosphere. Subsequently, lithium bis(trimethylsilyl)amide (LHMDS, 1.3 mL of 1 M solution in THF, 1.3 mmol) was added dropwise and the reaction mixture was stirred for 4 h at −78 °C. The resulting mixture was warmed to room temperature and aq. NH_4Cl (10 mL) was added, before extraction with EtOAc (3 × 20 mL). The combined organic extracts were washed with aq. $NaHCO_3$ (10 mL) and brine (10 mL) and dried over anhydr. Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography (hexane-EtOAc 7:3 v/v). TLC (hexane/EtOAc 7:3, eluted four times) of the reaction crude showed three components with $R_f = 0.30$, 0.24, and 0.20. The fraction with $R_f = 0.30$ (major diastereoisomer) was isolated and recrystallized from hexane-EtOAc (2:1 v/v) to afford 185 mg (44% yield) of *rac*-**6a** as colorless crystals with mp 154–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 1.31 (3H, t, $J = 6.7$ Hz, CH_3), 1.33 (3H, t, $J = 7.4$ Hz, CH_3), 2.33–2.54 (4H, m, 2 × CH_2), 3.27 (1H, t, $J = 12.5$ Hz, NCH_{ax}H diastereotopic proton), 4.21 (2H, q, $J = 7.1$ Hz, OCH_2), 4.32 (2H, q, $J = 7.1$ Hz, OCH_2), 4.51 (1H, dd, $J = 4.8$, 13.3 Hz, NCH_{eq}H diastereotopic proton), 5.22 (1H, br s, OH), 7.46–7.55 (3H, m, H_{ar}), 7.76–7.80 (1H, m, H_{ar}). ^{13}C NMR (100.5 MHz, $CDCl_3$) 14.0 (CH_3), 14.1 (CH_3), 27.2 (CH_2), 36.5 (NCH_2), 40.8 (CH), 48.8 (CH), 61.1 (OCH_2), 62.0 (OCH_2), 84.8 (C–OH), 121.8 (CH_{ar}), 123.8 (CH_{ar}), 129.8 (CH_{ar}), 130.6 (C_{ipso}), 132.3 (CH_{ar}), 146.7 (C_{ipso}), 164.9 (NC=O), 171.5 (OC=O), 174.5 (OC=O). FT-IR/ATR ν cm^{-1}: 3277, 3181, 2986, 2945, 2910, 1720, 1673, 1468, 1417, 1383,

1315, 1273, 1254, 1181, 1094, 1035, 1018, 900, 763, 695, 558, 512. HRMS (ESI-TOF): *m/z* calculated for $C_{18}H_{21}NO_6$ + H: 348.1442; [M + H^+]; found: 348.1446.

3.2.7. Triethyl (1R,2S,3S,10bS)-10b-hydroxy-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindole-1,2,3-tricarboxylate, (rac-**7**)

The procedure described above was followed with **2** (250 mg, 1.01 mmol), diethyl fumarate (0.25 mL, 1.51 mmol), and LiHMDS solution 1 M (1.3 mL, 1.3 mmol). The crude product was purified by column chromatography (hexane/EtOAc 7:3 *v/v*) to afford 280 mg (66% yield) of *rac*-**7** as a colorless solid mp = 138–140 °C, R_f = 0.25 (hexane/EtOAc 1:1 *v/v*). ^{1}H NMR (400 MHz, $CDCl_3$) 1.21 (3H, t, *J* = 7.1 Hz, CH_3), 1.27 (3H, t, *J* = 7.1 Hz, CH_3), 1.28 (3H, t, *J* = 7.1 Hz, CH_3), 2.56 (1H, d, *J* = 12.1 Hz, CH_{ax}), 2.81 (1H, td, *J* = 5.2, 11.9 Hz, CH_{ax}), 3.23 (1H,dd, *J* = 12.3, 13.2 Hz, NC*H*$_{ax}$H), 3.57 (1H, t, *J* = 12.0 Hz, CH_{ax}), 4.01–4.26 (5H, m, OCH_2), 4.29–4.37 (1H, m, OCH_2), 4.47 (1H, dd, *J* = 5.2, 13.2 Hz, NCH*H*$_{eq}$), 5.30 (br s, 1H, OH), 7.36–7.39 (1H, m, H_{ar}), 7.45–7.54 (2H, m, H_{ar}), 7.71–7.74 (1H, m, H_{ar}). ^{13}C NMR (100.5 MHz, $CDCl_3$) 13.9 (2 × CH_3), 14.0 (CH_3), 35.7 (NCH_2), 43.6 (CH), 43.7 (CH), 51.2 (CH), 61.4 (2 × OCH_2), 62.2 (OCH_2), 84.8 (C–OH), 121.9 (CH_{ar}), 123.9 (CH_{ar}), 130.0 (CH_{ar}), 130.4 (C_{ipso}), 132.3 (CH_{ar}), 145.8 (C_{ipso}), 164.5 (NC═O), 170.5 (OC═O), 171.3 (OC═O), 172.5 (OC═O). FT-IR/ATR *ν* cm^{-1}: 3268, 2986, 2936, 2910, 1738, 1723, 1677, 1470, 1426, 1396, 1375, 1314, 1213, 1178, 1113, 1091, 1011, 769, 697, 669, 567. HRMS (ESI-TOF): *m/z* calculated for $C_{21}H_{25}NO_8$ + H^+: 420.1653; found: 420.1649.

3.3. Preparation of compounds rac-**3a-b**, rac-**4a,d** and rac-**6a-c** under solvent-free ball-milling conditions

3.3.1. 1-Ethyl-3-methyl-(1S,3S,9bR)- and (1R,3R,9bS)-9b-hydroxy-5-oxo-3-phenyl-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindole-1,3-dicarboxylate, (rac-**3a**)

A mixture of phthalimide *rac*-**1** (200 mg, 0.677 mmol), ethyl acrylate (110 μL, 1.02 mmol), and cesium carbonate (242 mg, 0.74 mmol) was milled in a stainless-steel milling vial with two 11 mm diameter balls at 25 Hz for 90 min. The resulting reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (30 mL) and dried over anhydr. Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography (hexane-EtOAc 8:2 v/v). TLC (hexane-EtOAc 7:3, eluted twice) of the reaction crude showed five products with R_f = 0.55, 0.45, 0.33, 0.25, 0.20. The fraction with R_f = 0.55 corresponded to starting material *rac*-**1** (28 mg was recovered). The fraction with R_f = 0.25 was isolated and recrystallized from hexane-EtOAc (2:1 v/v) to give 42 mg (16% yield) of *rac*-**3a** as a colorless solid with mp 160–162 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 1.36 (3H, t, *J* = 7.2 Hz, CH_3), 3.27 (1H, dd, *J* = 7.2, 13.0 Hz, CH*H*), 3.35 (br s, 1H, OH), 3.41 (1H, t, *J* = 12.7 Hz, C*H*H), 3.58 (1H, dd, *J* = 7.2, 12.4 Hz, CH), 3.66 (3H, s, OCH_3), 4.25–4.37 (2H, m, OCH_2), 7.29–7.39 (3H, m, H_{ar}), 7.50–7.58 (3H, m, H_{ar}), 7.65 (1H, t, *J* = 7.5 Hz, H_{ar}), 7.80 (1H, d, *J* = 7.5 Hz, H_{ar}), 7.85 (1H, d, *J* = 7.5 Hz, H_{ar}). ^{13}C NMR (100.5 MHz, $CDCl_3$) 14.2 (CH_3), 44.6 (CH_2), 49.2 (CH), 53.1 (OCH_3), 61.6 (OCH_2), 68.5 (C), 95.8 (C–OH), 123.8 (CH_{ar}), 124.1 (CH_{ar}), 127.1 (2 × CH_{ar}), 127.7 (CH_{ar}), 128.0 (2 × CH_{ar}), 130.3 (CH_{ar}), 131.6 (C_{ipso}), 133.3 (CH_{ar}), 140.7 (C_{ipso}), 145.6 (C_{ipso}), 169.1 (NC═O), 169.9 (OC═O), 172.0 (OC═O).

3.3.2. Ethyl 1-methyl-(RS)-2-(1,3-dioxoisoindolin-2-yl)-2-phenylpentanedioate (rac-**3b**)

The fraction with R_f = 0.45 of the chromatographic profile of *rac*-**3a** was isolated to give 94 mg (35% yield) of *rac*-**3b** as a colorless solid with mp 97–99 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 1.19 (3H, t, *J* = 7.1 Hz, CH_3), 2.39–2.58 (2H, m, CH_2), 2.98–3.17 (2H, m, CH_2), 3.72 (3H, s, OCH_3), 4.03 (2H, qd, *J* = 2.1, 7.1 Hz, OCH_2), 7.29–7.43 (3H, m, H_{ar}), 7.53–7.55 (2H, m, H_{ar}), 7.72–7.75 (2H, m, H_{ar}), 7.79–7.82 (2H, m, H_{ar}) ^{13}C NMR (100.5 MHz, $CDCl_3$) 14.1 (CH_3), 29.3 (CH_2), 29.8 (CH_2), 53.0 (OCH_3), 60.5 (OCH_2), 66.7 (C_q), 123.4 (2 × CH_{ar}), 127.0 (2 × CH_{ar}), 128.1 (CH_{ar}), 128.2 (2 × CH_{ar}), 131.5 (C_{ipso}), 134.3 (2 × CH_{ar}), 136.3 (C_{ipso}), 167.9 (NC═O), 170.0 (OC═O), 172.6 (OC═O). FT-IR/ATR *ν* cm^{-1}: 3435, 3387, 2993, 2953, 1783, 1728, 1711, 1470, 1434, 1375, 1247, 1226, 1114, 973, 902, 850, 720, 698, 649, 614. HRMS (ESI-TOF) calculated for $C_{22}H_{21}NO_6$ + H^+: 396.1442; [M + H^+]; found: 396.1443.

The rest of the fractions afforded 88 mg (33% yield) of a mixture of diastereoisomeric products (*rac*-**3a** as the main component and two more polar compounds).

3.3.3. Methyl (1R,3S,9bR)- and (1S,3R,9bS)-1-cyano-9b-hydroxy-5-oxo-3-phenyl-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindole-3-carboxylate, (rac-**4a**)

A mixture of *rac*-**1** (200 mg, 0.677 mmol), acrylonitrile (67 μL, 1.02 mmol), and cesium carbonate (242 mg, 0.74 mmol) was milled in a stainless-steel milling vial with two 11 mm diameter balls at 25 Hz for 90 min. After the milling was complete, the resulting reaction mixture was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were washed with brine (30 mL) and dried over anhydr. Na_2SO_4. The solvent was evaporated under vacuum and the residue was purified by column chromatography (hexane-EtOAc 8:2 v/v). TLC (hexane-EtOAc 7:3, eluted three times) of the reaction crude showed four components with R_f = 0.70, 0.38, 0.25, 0.20. The fraction with R_f = 0.70 corresponded to starting material *rac*-**1** (60 mg was recovered). The fraction with R_f = 0.38 was isolated and recrystallized from hexane-EtOAc (2:1 v/v) to afford 70 mg (30% yield) of *rac*-**4a** as a colorless solid with mp 245–246 °C. ^{1}H NMR (400 MHz, $CDCl_3$): 2.95 (1H, br s, OH), 3.40 (1H, dd, *J* = 7.5, 12.1 Hz, C*H*H), 3.45 (1H, t, *J* = 11.7 Hz, CH*H*), 3.55 (1H, dd, *J* = 7.6, 11.1 Hz, CH), 3.69 (3H, s, OCH_3), 7.33–7.46 (5H, m, H_{ar}), 7.64 (1H, t, *J* = 7.5 Hz, H_{ar}), 7.73 (1H, t, *J* = 7.5 Hz, H_{ar}), 7.83 (1H, d, *J* = 7.2 Hz, H_{ar}), 7.84 (1H, d, *J* = 7.4 Hz, H_{ar}). ^{13}C NMR (100.5 MHz, $CDCl_3$) 36.2 (CH), 45.6 (CH_2), 53.5 (OCH_3), 69.0 (C), 95.0 (C–OH), 116.2 (CN), 122.7 (CH_{ar}), 124.7 (CH_{ar}), 126.9 (2 × CH_{ar}), 128.1 (CH_{ar}), 128.3 (2 × CH_{ar}), 131.2 (C_{ipso}), 131.4 (CH_{ar}), 134.1 (CH_{ar}), 139.8 (CH_{ar}), 143.8 (CH_{ar}), 168.6 (NC═O), 171.5 (OC═O). HRMS (ESI-TOF): *m/z* calculated for $C_{20}H_{16}N_2O_4$ + H^+: 349.1183; [M + H^+]; found: 349.1187.

3.3.4. Methyl (1R,3R,9bS)- and (1S,3S,9bR)-1-cyano-9b-hydroxy-5-oxo-3-phenyl-2,3,5,9b-tetrahydro-1H-pyrrolo[2,1-a]isoindole-3-carboxylate, (rac-**4d**)

The fractions with R_f = 0.25, and 0.20 afforded 70 mg (30% yield) of a mixture of diastereoisomers *rac*-**4b** and *rac*-**4d**. This mixture was recrystallized from hexane-EtOAc (2:1 v/v) to yield 15 mg (6% yield) of *rac*-**4d** (the more polar diastereoisomer) as colorless crystals with mp 234–236 °C. ^{1}H NMR (400 MHz, Acetone-d_6) 3.47 (1H, dd, *J* = 8.0, 13.9 Hz, CHH), 3.59 (3H, s, OCH_3), 3.62 (1H, d, *J* = 13.8 Hz, CHH), 4.01 (1H, d, *J* = 7.8 Hz, CH), 6.04 (1H, br s, 1H, OH), 7.28–7.44 (3H, m, H_{ar}), 7.49–7.61 (3H, m, H_{ar}), 7.75–7.90 (1H, m, H_{ar}), 7.75–7.82 (3H, m, H_{ar}). ^{13}C NMR (100.5 MHz, Acetone-d_6): 36.2 (CH), 45.6 (CH_2), 53.5 (OCH_3), 68.9 (C), 95.0 (C–OH), 116.5 (CN), 124.27 (CH_{ar}), 124.3 (CH_{ar}), 128.16 (2 × CH_{ar}), 128.18 (CH_{ar}), 128.4 (2 × CH_{ar}), 131.4 (CH_{ar}), 133.4 (C_{ipso}), 134.2 (CH_{ar}), 142.0 (C_{ipso}), 144.6 (C_{ipso}), 166.9 (NC═O), 171.5 (OC═O). HRMS (ESI-TOF) calculated for $C_{20}H_{16}N_2O_4$ + H^+: 349.1183; [M + H^+]; found: 349.1187.

3.3.5. Diethyl (1R,3S,10bS)- and (1S,3R,10bR)-10b-hydroxy-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindole-1,3-dicarboxylate, (rac-**6a**)

A mixture of phthalimide (200 mg, 1.36 mmol), ethyl acrylate (0.59 mL, 5.44 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene

Table 3
Crystallographic parameters.

	rac-**3a**	*rac*-**4c**	*rac*-**4d**	*rac*-**6a**	*rac*-**6b**	*rac*-**6c**	*rac*-**7**
Crystal data							
Chemical formula	C_{22} H_{21} N_1 O_6	$C_{20}H_{16}N_2O_4$	$C_{20}H_{16}N_2O_4$	$C_{18}H_{21}NO_6$	$C_{18}H_{21}NO_6$	$C_{18}H_{21}N_1O_6$	$C_{20}H_{16}N_2O_4$
M_r	395.40	348.35	348.35	347.36	347.36	347.36	348.35
Crystal system, space group	Monoclinic, $P2_1$	Monoclinic, $P2_{1/n}$	Monoclinic, $P2_1/_c$	Monoclinic, $P2_1/_c$	Triclinic, P-1	Monoclinic, $P2_1/_c$	Monoclinic, $P2_{1/n}$
Temperature (K)	293	150.04	277.65	150.01	296.55	293.15	150.04
a,b,c (Å)	7.862(2)	9.1818(4)	11.1814(4)	10.8580 (7)	8.6977(4)	10.695(3)	9.1818(4)
	10.4940(18)	14.7107(6)	18.0521 (6)	15.1246 (9)	9.9451(4)	15.603(3)	14.7107(6)
	12.4268(16)	12.7544(5)	8.7783 (3)	10.3651 (6)	11.1513(5)	10.743(2)	12.7544(5)
V (Å^3)	1003.8 (4)	1657.48(12)	1713.80	1696.26(18)	879.15(7)	1791.7 (7)	1657.48(12)
Z	2	4	4	4	2	4	4
Radiation type	CuKα(λ = 1.54178)	CuKα(λ = 1.54178)	CuKα(λ = 1.54178)	MoKα(λ = 0.71073)	CuKα(λ = 1.54178)	CuKα(λ = 1.54178)	CuKα(λ = 1.54178)
μ (mm^{-1})	0.795	0.813	0.787	0.103	0.825	0.810	0.813
Cristal size (mm)	0.39 × 0.28 x 0.15	0.36 × 0.29 x 0.25	0.31 × 0.25 x 0.17	0.62 × 0.32 × 0.29	0.36 × 0.31 × 0.17	0.34 × 0.31 x 0.10	0.36 × 0.29 x 0.25
Data collection							
Diffractometer	Bruker D8 VENTURE diffractometer						
Absortion correction	Multiscan SADABS-2014/5 (Bruker,2014/5)						
T_{min}, T_{max}	0.6867, 0.7530	0.6540, 0.7536	0.6991, 0.7538	0.6504, 0.7457	1.000,0.9265	0.6867, 0.7530	0.6540, 0.7536
No. of measured, independent and observed [I > 2>(*I*)] reflections	9723,3314,3034	80504, 3231,3115	106123, 3503, 3119	70806, 4186, 4186	8831, 2850, 2850	9723,3314,3034	80504, 3231,3115
R_m (sin θ/λ)$_{max}$ (Å^{-1})							
Refinement							
R[F^2 > 2> (F^2)], w*R*(F^2), *S*	0.029, 0.070, 1.062	0.0408, 0.1010, 1.043	0.0373, 0.0969, 1.046	0.0459, 0.1033, 1.056	0.0512, 0.1344 1.060	0.029, 0.070, 1.062	0.0408, 0.1010, 1.043
No. of reflections	3314	3231	3503	4186	8831	3314	3231
No. of parameters	266	238	241	230	258	266	238
No. of restrains	1	0	0	0	0	1	0
H-atom treatment	H atoms treated by a mixture of independent and constrained refinement						
Largest diff. Peak/hole/e Å^{-3}	0.10/-0.11	0.26/-0.21	0.21/-0.19	0.64/-0.37	0.20/-0.23	0.10/-0.11	0.26/-0.21

Computer programs: *SAINT* v8.37A (Bruker, 2015), ShelXT (Sheldrick, 2015), *SHELXL* (Sheldrick, 2015), Olex2 (Dolomanov et al., 2009).

(DBU, 0.22 mL, 1.5 mmol) was milled in a stainless-steel milling vial with two 11 mm diameter balls at 25 Hz for 90 min. Subsequently, sodium hydride 60% (dispersion in mineral oil, 60 mg, 1.5 mmol) was added into the milling vial and grinding was continued at 25 Hz for 90 min. Following this, the resulting reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were washed with brine (30 mL) and with a saturated aqueous $NaHCO_3$ solution (30 mL), before drying over anh. Na_2SO_4. The solvent was removed under vacuum and the residue was purified by column chromatography (hexane-EtOAc 8:2 v/v). TLC (hexane-EtOAc 7:3, eluted four times) of the reaction crude showed four components with $R_f = 0.83$, 0.30, 0.24, 0.20. The fraction with $R_f = 0.83$ corresponded to starting material **2** (30 mg was isolated). The fraction with $R_f = 0.30$ was isolated and recrystallized from hexane-EtOAc (2:1 v/v) to afford 152 mg (32% yield) of *rac*-**6a** as colorless crystals with mp 154–156 °C. ^{1}H NMR (400 MHz, $CDCl_3$) 1.28 (3H, t, $J = 7.1$ Hz, CH_3), 1.31 (3H t, $J = 7.1$ Hz, CH_3), 2.31–2.54 (4H, m, 2 × CH_2, CH_2), 3.26 (1H, dd, $J = 11.9$, 13.2 Hz, NC*H*$_{ax}$H diastereotopic proton), 4.19 (2H, qd, $J = 0.8$, 7.1 Hz, OCH_2), 4.30 (2H, q, $J = 7.1$ Hz, OCH_2), 4.50 (1H, ddd, $J = 1.2$, 5.3, 13.4 Hz, NCH*H*$_{eq}$ (diastereotopic proton), 5.22 (1H, br s, OH), 7.45–7.54 (3H, m, H_{ar}), 7.75–7.78 (1H, m, H_{ar}). ^{13}C NMR (100.5 MHz, $CDCl_3$) 14.0 (CH_3), 14.1 (CH_3), 27.2 (CH_2), 36.5 (NCH_2), 40.8 (CH), 48.8 (CH), 61.1 (OCH_2), 62.0 (OCH_2), 84.8 (C–OH), 121.8 (CH_{ar}), 123.8 (CH_{ar}), 129.8 (CH_{ar}), 130.6 (C_{ipso}), 132.3 (CH_{ar}), 146.7 (C_{ipso}), 164.9 (NC═O), 171.5 (OC═O), 174.5 (OC═O). HRMS (ESI-TOF): *m*/*z* calculated for $C_{18}H_{21}NO_6 + H^+$: 348.1442; [M + H$^+$]; found: 348.1442.

The rest of the fractions afforded 140 mg (30% yield) of a mixture of diastereoisomeric products (rac-**6a**, rac-**6b**, and rac-**6c**). This diastereoisomeric mixture was separated by column chromatography.

3.3.6. Diethyl (1R,3R,10bR)- and (1S,3S,10bS)-10b-hydroxy-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindole-1,3-dicarboxylate, (rac-**6b**)

Diastereoisomer *rac*-**6b** with $R_f = 0.24$ was isolated and recrystallized from hexane-EtOAc (2:1 v/v) as colorless crystals with mp 130–132 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 0.72 (3H, t, $J = 7.1$ Hz, CH_3), 1.27 (3H, t, $J = 7.2$ Hz, CH_3), 2.22 (1H, apparent ddt, $J = 1.8$, 3.6, 13.8 Hz, C*H*$_{eq}$H, diastereotopic proton), 2.47 (1H, td, $J = 5.0$, 13.5 Hz, CH*H*$_{ax}$, diastereotopic proton), 2.97 (1H, apparent tt, $J = 4.3$, 12.3 Hz, CH_{ax}), 3.09 (1H, t, $J = 12.5$ Hz, NC*H*$_{ax}$H, diastereotopic proton), 3.39 (1H, dd, $J = 2.2$, 4.9 Hz, CH_{eq}), 3.61 (2H, qd, $J = 1.3$, 7.1 Hz, OCH_2), 4.16 (2H, qd, $J = 1.6$, 7.1, OCH_2), 4.18 (1H, ddd, $J = 1.5$, 5.1, 12.8 Hz, NCH*H*$_{eq}$, diastereotopic proton), 4.33 (1H, br s, OH), 7.31–7.34 (1H, m, H), 7.38–7.40 (1H, m, H_{ar}), 7.49–7.52 (1H, m, H_{ar}), 7.55–7.56 (1H, m, H_{ar}). ^{13}C NMR (125.7 MHz, $CDCl_3$) 13.4 (CH_3), 14.2 (CH_3), 25.3 (CH_2), 36.2 (CH), 36.5 (NCH_2), 46.4 (CH), 60.4 (OCH_2), 60.8 (OCH_2), 85.2 (C–OH), 122.1 (CH_{ar}), 123.0 (CH_{ar}), 129.6 (CH_{ar}), 131.4 (C_{ipso}), 131.9 (CH_{ar}), 145.3 (C_{ipso}), 165.8 (NC═O), 170.3 (OC═O), 172.6 (OC═O). HRMS (ESI-TOF): *m*/*z* calculated for $C_{18}H_{21}NO_6 + H^+$: 348.1442; [M + H$^+$]; found: 348.1442.

3.3.7. Diethyl (1R,3R,10bS)- and (1S,3S,10bR)-10b-hydroxy-6-oxo-1,2,3,4,6,10b-hexahydropyrido[2,1-a]isoindole-1,3-dicarboxylate, (rac-**6c**)

Diastereoisomer *rac*-**6c** with $R_f = 0.20$ was isolated and recrystallized from hexane-EtOAc (2:1 v/v) as colorless crystals with mp 150–152 °C. ^{1}H NMR (500 MHz, $CDCl_3$) 1.22 (3H, t, $J = 7.1$ Hz, CH_3), 1.31 (3H, t, $J = 7.2$ Hz, CH_3), 2.37 (1H, ddd, $J = 4.6$, 12.6, 13.4 Hz, C*H*$_{ax}$H, diastereotopic proton), 2.41 (1H, apparent ddt, $J = 2.1$, 4.2, 13.5 Hz, CH*H*$_{eq}$ diastereotopic proton), 2.83 (1H, apparent dt, $J = 2.1$, 4.3 Hz, CH_{eq}), 2.92 (1H, dd, $J = 4.3$, 12.6 Hz, CH_{ax}), 3.42 (1H, dd, $J = 4.6$, 13.6 Hz, C*H*$_{ax}$H, diastereotopic proton), 4.06–4.17 (2H, m, OCH_2), 4.25–4.36 (2H, m, OCH_2), 4.67 (1H, dt, $J = 1.6$, 13.6 Hz,

CHH_{eq}), 5.26 (1H, br s, OH), 7.44–7.53 (3H, m, H_{ar}), 7.75–7.78 (1H, m, H_{ar}). ^{13}C NMR (125.7 MHz, $CDCl_3$) 14.06 (CH_3), 14.08 (CH_3), 25.8 (CH_2), 36.3 (NCH_2), 37.9 (CH), 45.5 (CH), 61.2 (OCH_2), 61.9 (OCH_2), 85.0 (C–OH), 121.6 (CH_{ar}), 123.9 (CH_{ar}), 129.6 (CH_{ar}), 130.7 (C_{ipso}), 132.1 (CH_{ar}), 147.1 (C_{ipso}), 164.8 (NC=O), 172.3 (OC=O), 175.4 (OC=O). HRMS (ESI-TOF): *m/z* calculated for $C_{18}H_{21}NO_6 + H^+$: 348.1442; $[M + H^+]$; found: 348.1439.

For the last 3 compounds, a final purification involving slow recrystallization (3 times) from hexane-EtOAc 1:1 was applied for X-Ray analysis.

4. Refinement of X-ray diffraction data

Crystal data, data collection and structure refinement details for compounds *rac*-**3a,** *rac*-**4c**-**d** and *rac*-**6a**-**c** and *rac*-**7** are summarized in Table 3 and included in ESI. All atoms were placed at the observed positions and refined with bond distances in line with ideal values. All hydrogen atoms were added at calculated positions and refined according to the ridding model, with isotropic parameters based on the parent atoms.

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Appendix A. Supplementary data

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