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Organocatalytic Michael addition of indanone carboxylates to vinyl selenone for the asymmetric synthesis of polycyclic pyrrolidines

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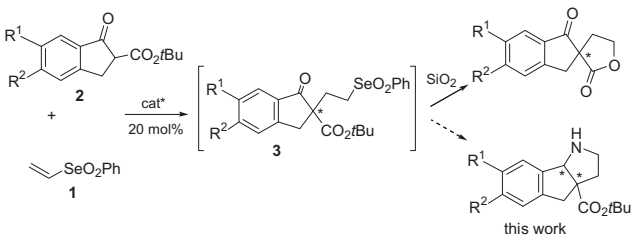
ABSTRACT

A Michael addition of racemic indanone carboxylates to vinyl selenone catalyzed by C6′hydroxyl cinchona derivatives is the key step of a synthetic sequence for a practical access to highly enantioenriched (up to 98% ee) polycyclic pyrrolidines bearing contiguous tertiary and quaternary stereocenters.

1. Introduction

Organoselenium compounds are nowadays considered versatile reagents for many synthetic transformations, which take advantage of the ease with which these compounds effect functional group interconversions. In the last years, they found many interesting applications in the stereoselective preparation of chiral molecules under mild and operationally simple reaction conditions.[1] Despite the explosion of organocatalysis, which has recently emerged as a robust and powerful strategy for the asymmetric construction of valuable building blocks and molecules of pharmaceutical interest, very few organocatalytic processes involving selenium reagents have been explored.[2] In this field, we have recently developed new enantioselective methods for the preparation of important classes of selenium compounds, such as α-selenocarbonyl derivatives.[3] Moreover, the ease of handling and the unique reactivity of vinyl selenones have been exploited in new organocatalytic strategies for the practical asymmetric construction of densely functionalized cyclic compounds from simple precursors.[4] An example is the Michael addition/cyclization sequence with the easily accessible cyclic β-ketoesters **2** and the vinyl selenone **1** catalyzed by C6′hydroxyl cinchona derivatives, which has been successfully employed for the enantioselective synthesis of spirolactones (Scheme 1).[4a] This practical one-pot sequence is based on the peculiar properties of the selenonyl moiety, which acts both as an electron-withdrawing group during the addition step and as a leaving group during the following cyclization. We now report that the same Michael adducts **3** are useful intermediates in the diastereo- and enantioselective synthesis of polycyclic pyrrolidines bearing a β-aminoester motif. These structures contain synthetically challenging contiguous tertiary and quaternary stereocenters.



Scheme 1.

In the last years novel strategies for the synthesis of compounds that incorporate a pyrrolidine ring have received considerable

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attention.[5–9] Properly substituted indenopyrrolidines **A** have been studied as hypoglycemic agents[6] or as antagonists of NMDA receptor (Fig. 1).[7] Proline derivatives **B** and conformationally restricted rivastigmine analogues **C** have been evaluated as angiotensin converting enzyme inhibitor analogues[8] or acetylcholinesterase inhibitors, respectively.[9] Moreover, in the last decade the asymmetric synthesis of β-aminoacids and derivatives has received great attention[10] and the development of new catalytic methodologies is particularly appreciated. Our method, which employs the easy to handle vinyl selenone for the key addition step, nicely complements procedures based on the catalytic 1,4-addition of cyclic β-ketoesters to nitroethylene followed by reduction and cyclization.[11]

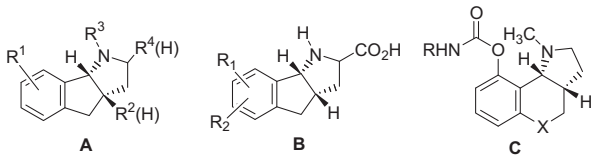


Fig. 1. General structures of biologically active polycyclic pyrrolidines.

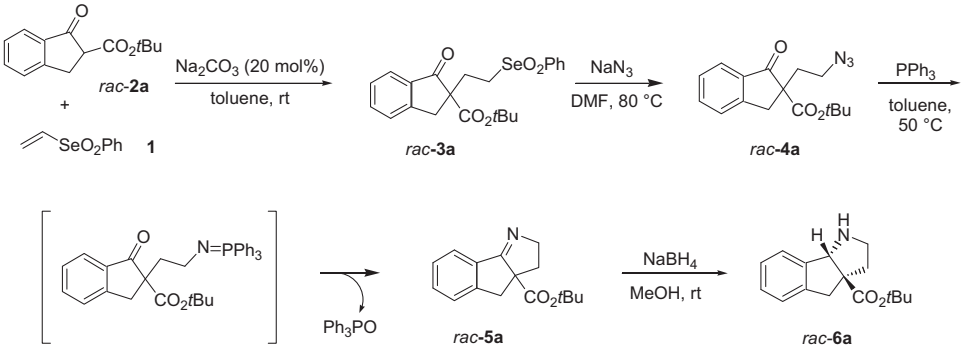
2. Results and discussion

For preliminary studies we chose the reaction of *tert*-butyl indanone carboxylate *rac*-**2a** (2 equiv) and the vinyl selenone **1**. When these compounds were treated in toluene with a catalytic amount of anhydrous Na_2CO_3 (Scheme 2) the Michael adduct *rac*-**3a** was formed quantitatively. We hypothesized that the conversion of **3a** into the corresponding alkyl azide could give access to indenopyrrolidines via a Staudinger/aza-Wittig sequence.[12] Due to the good leaving group properties of the phenylselenonyl unit, the nucleophilic substitution was complete after 1 h and *rac*-**4a** was isolated after column chromatography in 80% yield. The cyclization by treatment with triphenylphosphine in toluene gave *rac*-**5a** in 78% yield in 1 h. The formation of the iminophosphorane intermediate was not observed because it rapidly reacts chemoselectively with the carbonyl group. In order to save time and resources, minimize the generation of chemical waste and reduce manual operations, the multi-reaction sequence was carried out excluding unnecessary purification processes. Thus, the crude *rac*-**3a** was used for the nucleophilic substitution after toluene evaporation and only an aqueous work-up was employed for the next DMF removal. Under these conditions *rac*-**5a** was isolated in 80% overall yield. Finally, the reduction was carried out with an excess of sodium borohydride in MeOH. Reductions of imines by hydride transfer are well documented, but most examples are restricted to nonhindered derivatives.[13] Although ^{1}H NMR analysis of the crude reaction mixture showed the complete conversion of the starting imine and the presence of *rac*-**6a** as the sole reaction product, it was recovered after column chromatography in acceptable 50% yield. The cis stereochemistry at the ring junction was assigned by a NOESY experiment. A diagnostic dipolar interaction between the ring junction hydrogen and the *tert*-butyl group was observed. Encouraged by these results, we focused on the asymmetric variant of the process (Table 1). In the previous report concerning the synthesis of spirolactones,[4a] we demonstrated that quinidine C6′-OH 9-*O*-(9′-phenanthryl) ether **C6′OH-QD** exhibits a high catalytic activity and an excellent enantiocontrol over the formation of addition product **3a**, which is also the key intermediate in the construction of the indeno pyrrolidine **6a**. Thus, the same bifunctional catalyst was used for the new cyclization sequence affording **5a** with an excellent enantiomeric excess (98% ee by chiral HPLC). Interestingly, decreasing of the catalyst loading from 20 mol % to 5 mol % do not affect the chemical and optical yields.[14] As expected, the reduction gave **6a** as a single diastereoisomer without loss of enantiomeric purity. The cyclization sequence and the following reduction were applied to some indanone derivatives bearing electron-withdrawing or electron-donating groups on the aromatic ring. Reaction conditions, chemical yields and enantiomeric excesses of the final products are reported in Table 1. The indenopyrrolidines were prepared with complete diastereoselectivity and high enantiomeric excesses. Both enantiomers are readily accessible. In fact replacement of catalyst **C6′OH-QD** with its pseudoenantiomer **C6′OH-Q** led to the formation of *ent*-**6a** and *ent*-**6b** in comparable yields and enantiomeric excesses (Table 1, entries 1 and 2). The method was extended to the trans Michael donor *rac*-**2e** containing an additional stereocenter and the compound **6e** was obtained as a single diastereoisomer in 95% ee. Under the usual conditions, the chiral catalyst not only controls the absolute configuration at the quaternary stereocenter formed during the addition but also reacts almost exclusively with one of the enantiomers of *rac*-**2e**.

Finally we try to adapt the strategy to the synthesis of benzoindoles (Table 1, entry 6), but compounds **5f** an **6f** were obtained in very poor stereoselectivities. A slow rate of reduction and a poor diastereoselectivity have been already observed in these ring systems.[13b]

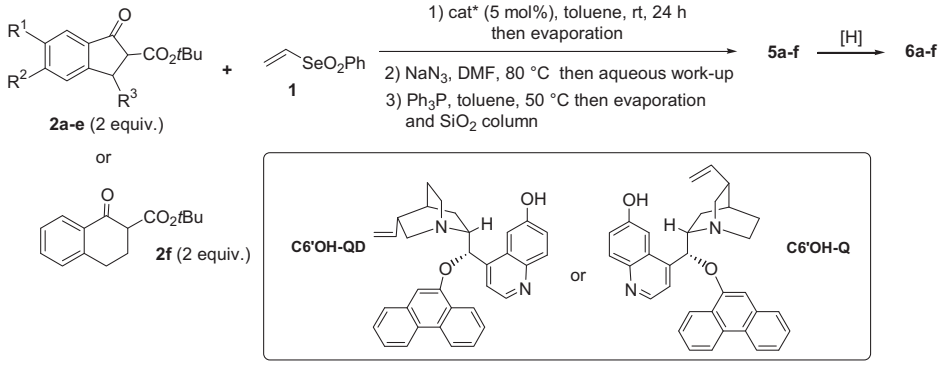
3. Conclusions

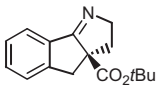
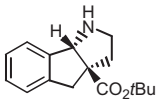
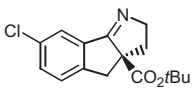
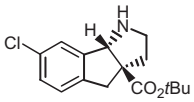
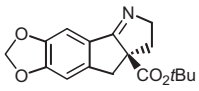
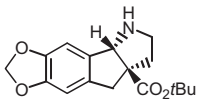
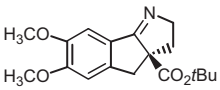
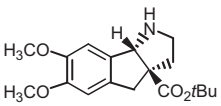
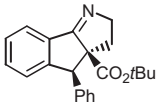
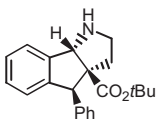
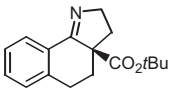
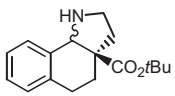
In conclusion a practical synthetic sequence for the asymmetric construction of indeno[1,2-*b*]pyrrolidines starting from easily available starting materials has been described. The reactions proceed with good chemical yields and generate compounds with



Scheme 2.

Table 1
Asymmetric synthesis of polycyclic pyrrolidines



Entry	Cyclic iminoester		Yield[a–c] %	Cyclic aminoester		Yield[b,c] %	ee %[d]
1		**5a** *ent*-**5a**[e]	65 65		**6a** *ent*-**6a**[e]	55 56	98 98
2		**5b** *ent*-**5b**[e]	85 65		**6b** *ent*-**6b**[e]	57 72	94 93
3		**5c**	74		**6c**	50	96
4		**5d**	—[f]		**6d**	44[g]	96
5		**5e**	60		**6e**	45 (70)[h]	95
6		**5f**	53		**6f**	40 (67)[h] dr 56:44	20[i]

[a] Unless otherwise specified, addition reactions were performed on a 0.4 mmol scale at room temperature with C6′OH-QD as the catalyst. **3a**–**f** and **4a**–**f** were not isolated.
[b] Yield of the isolated product.
[c] The absolute configurations at the quaternary stereocenter were assigned according to Ref. 4a. The remaining stereogenic centres were assigned considering the relative configuration established for **6a** and **6e** by NOESY correlations.
[d] ee values of the aminoesters were determined after Boc-protection by HPLC analysis on a chiral stationary phase.
[e] Obtained by using the catalyst C6′OH-Q.
[f] Not determined because the isolated product was impure of Ph_3PO.
[g] Overall yield calculated on the starting vinyl selenone **1**.
[h] Yield in brackets is based on recovered starting material.
[i] The ee was determined on the imine **5f**.

adjacent tertiary and quaternary stereocenters with an excellent diastereo and enantiocontrol. Further studies to expand the synthetic applications of the present sequence are currently underway.

4. Experimental section

4.1. General

^1H and ^{13}C NMR were recorded in $CDCl_3$ at 400 and 100 MHz or at 200 and 50.3 MHz on a Bruker Avance-DRX 400 or a Bruker Avance DR 200, respectively. Chemical shifts (δ) are reported in parts per million relative to residual solvent signals ($CHCl_3$, 7.26 ppm for ^1H NMR, $CDCl_3$, 77.0 ppm for ^{13}C NMR). Coupling constants are given in hertz. The following abbreviations are used to indicate the multiplicity: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad signal. GC–MS analyses were carried out with an HP 6890 gas chromatograph (HP-5MS capillary column, 30 m, I.D. 0.25 mm, film 0.25 μm) equipped with an HP 5973 Mass Selective Detector at an ionizing voltage of 70 eV. IR spectra were recorded with a Jasco model 410 spectrometer

equipped with a diffuse reflectance accessory. High resolution mass spectra (HRMS) were recorded on Agilent 6540-UHD Accurate Mass Q-TOF LC/MS instrument. Optical rotations were measured with a Jasco DIP-1000 digital polarimeter, the concentrations (c) are reported in gram per 100 mL. Chiral HPLC analyses were performed on an HP 1100 series instrument equipped with Chiralcel OD-H (250×4.6 mm), Lux amylose-2 (250×4.6 mm) or Lux cellulose-2 (250×4.6 mm) columns and an UV detector. Thin layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck) on aluminium sheets. Reaction products were purified by column chromatography performed on Merck silica gel 60 (70–230 mesh). Deactivated silica gel was prepared by washing the silica gel with a 5% suspension of $NaHCO_3$ in MeOH. After removal of the solvent, the silica gel was oven-dried at 150 °C.

4.2. Starting material

Commercial grade solvents and reagents were used without further purification. Starting vinyl selenone **1** was prepared from the corresponding selenide by oxidation with an excess of *m*-chloroperbenzoic acid (*m*-CPBA) in dichloromethane.[15] Racemic *tert*-butyl β-ketoesters **2a**–**f** were prepared from the corresponding ketones (Aldrich Inc.) by deprotonation with NaH in THF, followed by treatment with *tert*-butyl 1*H*-pyrrole-1-carboxylate.[16] The catalysts were prepared according to literature procedures.[17]

4.3. One-pot synthesis of cyclic imines 5: general procedure

Vinyl selenone **1** (0.4 mmol) and **C6′OH-QD** or **C6′OH-Q** (0.02 mmol, 5 mol %) were dissolved in toluene (1.6 mL). The β-ketoester *rac*-**2a**–**f** (0.8 mmol, 2 equiv) was added at room temperature and the resulting solution was stirred for 24 h. Toluene was removed under reduced pressure, then DMF (1.6 mL) and NaN_3 (0.8 mmol, 2 equiv) were added and the reaction was warmed at 80 °C. The progress of the reaction was monitored by TLC analysis. The reaction was stirred until **3a**–**f** was completely consumed (1–2 h). The reaction mixture was cooled to room temperature, poured into water (15 mL) and extracted with Et_2O (3×15 mL). The ethereal layers were washed with brine, dried over Na_2SO_4 and evaporated under reduced pressure. The crude mixture was dissolved in toluene, then Ph_3P (0.52 mmol, 1.3 equiv) was added at room temperature. When nitrogen evolution had ceased, the mixture was warmed to 50 °C. The progress of the reaction was monitored by TLC. After 1–2 h the solvent was evaporated and the residue was purified by column chromatography. Physical and spectral data of compounds **5a**–**f** are reported below. Racemic compounds for HPLC analyses were prepared with the same procedure using Na_2CO_3 (0.08 mmol, 20 mol %) as catalyst in the first step. The intermediate azide *rac*-**4a** was isolated and characterized by ^1H and ^{13}C.

4.4. *tert*-Butyl (3a*R*)-2,4-dihydroindeno[1,2-*b*]pyrrole-3a(3*H*) carboxylate (5a)

This compound was isolated as an oil by column chromatography (elution gradient: light petroleum/ethyl acetate 90:10 to 80:20) in 65% yield and 98% ee as determined by HPLC analysis [Lux cellulose-2, hexane/IPA 99:1, 1.0 mL/min, λ 230 nm, *t* (major enantiomer)=19.9 min, *t* (minor enantiomer)=21.6 min]. $[\alpha]_D^{27}=-16.5$ (*c* 0.68, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.76–7.74 (m, 1H, CH), 7.42–7.27 (m, 3H, CH), 4.41 (dd, 2H; *J*=3.1, 9.1 Hz, CH_2N), 3.55 (d, 1H; *J*=15.6 Hz, CH_2N), 2.71 (d, 1H; *J*=15.6 Hz, CH_2), 2.59 (td, 1H; *J*=3.1, 12.5 Hz, CH_2CH_2N), 2.1 (td, 1H; *J*=9.1, 12.5 Hz, CH_2CH_2N), 1.32 (s, 9H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ=182.5, 171.0, 151.7, 132.6, 131.4, 127.3, 125.8, 123.1, 81.4, 68.0, 67.2, 38.7, 37.0, 27.7 (3C). MS (70 eV, EI): *m*/*z* (%): 257 (9) [M^+], 201 (87), 184 (19), 157 (44), 156 (100), 129 (37), 128 (46), 127 (25), 116 (12), 57 (79). FT-IR (KBr): ν 1716.8 (C=O), 1652.7 (C=N) cm^{-1}.

4.5. *tert*-Butyl (3a*R*)-7-chloro-2,4-dihydroindeno[1,2-*b*]pyrrole-3a(3*H*)-carboxylate (5b)

This compound was isolated as an oil by column chromatography (elution: light petroleum/ethyl acetate 85:15) in 85% yield. $[\alpha]_D^{28}=-18.9$ (*c* 0.98, $CHCl_3$); ^1H NMR (200 MHz, $CDCl_3$, 25 °C): δ=7.77–7.66 (m, 1H, CH), 7.40–7.20 (m, 2H, CH), 4.41 (dd, 2H; *J*=3.1, 9.1 Hz, CH_2N), 3.51 (d, 1H; *J*=15.6 Hz, CH_2), 2.65 (d, 1H; *J*=15.6 Hz, CH_2), 2.59 (td, 1H; *J*=3.1, 12.5 Hz, CH_2CH_2N), 1.99 (td, 1H; *J*=9.1, 12.5 Hz, CH_2CH_2N), 1.33 (s, 9H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ=181.1, 170.7, 149.8, 134.2, 133.3, 131.3, 126.9, 123.2, 81.8, 68.4, 67.3, 38.2, 37.0, 27.7 (3C). MS (70 eV, EI): *m*/*z* (%): 293 (2) [M^++2], 291 (7) [M^+], 237 (41), 236 (21), 235 (88), 218 (16), 192 (51), 191 (41), 190 (100), 156 (22), 155 (35), 154 (32), 128 (31), 127 (35), 57 (100). FT-IR (KBr): ν 1717 (C=O), 1661 (C=N) cm^{-1}.

4.6. *tert*-Butyl (7a*R*)-6,8-dihydro[1,3]dioxolo[5,6]indeno[1,2-*b*]pyrrole-7a(7*H*)-carboxylate (5c)

This compound was isolated as an oil by column chromatography (elution: light petroleum/ethyl acetate 85:15) in 74% yield. $[\alpha]_D^{28}=-37.3$ (*c* 1.75, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.14 (s, 1H, CH), 6.78 (s, 1H, CH), 6.04–6.0 (m, 2H, CH_2O), 4.39–4.34 (m, 2H, CH_2N), 3.43 (d, 1H; *J*=15.3 Hz, CH_2), 2.60 (d, 1H; *J*=15.3 Hz, CH_2), 2.53 (ddd, 1H; *J*=2.2, 3.8, 12.4 Hz, CH_2CH_2N), 1.97 (td, 1H; *J*=9.1, 12.4 Hz, CH_2CH_2N), 1.35 (s, 9H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ=181.5, 171.2, 150.9, 147.6, 147.4, 126.1, 106.0, 102.8, 101.7, 81.5, 68.5, 66.8, 38.5, 36.8, 27.7 (3C). MS (70 eV, EI): *m*/*z* (%): 301 (30) [M^+], 245 (68), 244 (28), 201 (47), 200 (100), 199 (20), 173 (30), 142 (17), 115 (30), 57 (44). FT-IR (KBr): ν 1718 (C=O), 1653 (C=N) cm^{-1}.

4.7. *tert*-Butyl (3a*R*)-6,7-dimethoxy-2,4-dihydroindeno[1,2-*b*] pyrrole-3a(3*H*)-carboxylate (5d)

This compound after column chromatography (elution: light petroleum/ethyl acetate 90:10) was impure of Ph_3P=O. ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.20 (s, 1H, CH), 6.80 (s, 1H, CH), 4.44–4.32 (m, 2H, CH_2N), 3.92 (s, 3H OCH_3), 3.90 (s, 3H OCH_3), 3.49 (d, 1H; *J*=15.2 Hz, CH_2), 2.64 (d, 1H; *J*=15.2 Hz, CH_2), 2.54 (ddd, 1H; *J*=1.5, 4.4, 12.5 Hz, CH_2CH_2N), 1.97 (ddd, 1H; *J*=8.4, 9.7, 12.5 Hz, CH_2CH_2N), 1.33 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=182.2, 171.4, 152.2, 149.0, 145.4, 124.6, 107.9, 104.9, 81.4, 68.3, 67.0, 56.0, 55.9, 38.4, 36.9, 27.8 (3C). MS (70 eV, EI): *m*/*z* (%): 317 (48) [M^+], 262 (21), 261 (82), 260 (49), 217 (36), 216 (100), 200 (21), 189 (24), 185 (18), 172 (12), 57 (33). FT-IR (KBr): ν 1713 (C=O), 1653 (C=N) cm^{-1}.

4.8. *tert*-Butyl (3a*S*,4*S*)-4-phenyl-2,4-dihydroindeno[1,2-*b*] pyrrole-3a(3*H*)-carboxylate (5e)

This compound was obtained as a single diastereoisomer and isolated as an oil by column chromatography (elution: light petroleum/ethyl acetate 70:30) in 60% yield. $[\alpha]_D^{21}=-127.0$ (*c* 1.20, $CHCl_3$); ^1H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.95–7.75 (m, 1H, CH), 7.48–7.10 (m, 8H, CH), 4.37 (s, 1H, CHPh), 4.28 (dd, 1H; *J*=7.5, 15.0 Hz, CH_2N), 4.0 (ddd, 1H; *J*=5.0, 11.0, 15.0 Hz, CH_2N), 2.84 (dd, 1H; *J*=5.0, 12.0 Hz, CH_2CH_2N), 2.05 (ddd, 1H; *J*=7.5, 11.0, 12.0 Hz, CH_2CH_2N), 0.95 (s, 9H, CH_3); ^{13}C NMR (50.3 MHz, $CDCl_3$, 25 °C): δ=182.4, 168.2, 152.1, 137.9, 135.0, 131.0, 129.2 (2C), 128.3 (2C), 127.9, 127.3, 126.3, 122.8, 81.4, 74.3, 65.4, 57.0, 37.2, 27.5 (3C). MS (70 eV, EI): *m*/*z* (%): 333 (19) [M^+], 277 (100), 276 (52), 260 (13), 233 (46),

232 (72), 200 (56), 156 (28), 154 (18), 57 (34). FT-IR (KBr): ν 1724 (C=O), 1657 (C=N) cm^{-1}.

4.9. *tert*-Butyl (3a*R*)-2,3,4,5-tetrahydro-3a*H*-benzo[*g*]indole-3a-carboxylate (5f)

This compound was isolated as an oil by column chromatography (elution gradient: light petroleum/diethyl ether 80:20 to 50:50) in 53% yield and 20% ee as determined by HPLC analysis [Lux cellulose-2, hexane/IPA 90:10, 1 mL/min, λ 230 nm, t (minor enantiomer)=4.8 min, t (major enantiomer)=5.6 min]. $[\alpha]_D^{27}$=+15.21 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=8.08 (dd, 1H; J=1.4, 7.5 Hz, CH), 7.3 (dt, 1H; J=1.4, 7.5 Hz, CH), 7.26 (t, 1H; J=7.5 Hz, CH), 7.2 (d, 1H; J=7.5 Hz, CH), 4.18 (ddd, 1H, J=1.0, 7.9, 15.6 Hz, CH_2N), 3.86 (ddd, 1H, J=6.8, 10.4, 15.6 Hz, CH_2N), 3.08 (ddd, 1H, J=5.1, 13.1, 17.7 Hz, CH_2), 2.86 (ddd, 1H, J=1.9, 5.2, 17.7 Hz, CH_2), 2.67 (ddd, 1H, J=1.9, 5.1, 13.1 Hz, CH_2), 2.47 (ddd, 1H; J=1.0, 6.8, 13.0 Hz, CH_2CH_2N), 1.94 (ddd, 1H; J=7.9, 10.4, 13.0 Hz, CH_2CH_2N), 1.80 (dt, 1H; J=5.2, 13.1 Hz, CH_2), 1.34 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=172.1, 171.4, 139.6, 130.5, 130.0, 128.6, 126.4, 126.0, 81.4, 59.9, 58.8, 37.6, 32.8, 27.8, 27.5 (3C). MS (70 eV, EI): m/z (%): 271 (7) [M^+], 215 (60), 171 (23), 170 (100), 128 (13), 115 (11), 57 (53). FT-IR (KBr): ν 1722 (C=O), 1626 (C=N) cm^{-1}.

4.10. *tert*-Butyl 2-(2-azidoethyl)-1-oxo-2-indanecarboxylate (*rac*-4a)

This compound was isolated as an oil by column chromatography (elution: light petroleum/ethyl acetate 95:5) in 80% yield. ^{1}H NMR (200 MHz, $CDCl_3$, 25 °C): δ=7.78 (m, 1H, CH), 7.70–7.35 (m, 3H, CH), 3.65 (d, 1H; J=17.2 Hz, CH_2), 3.50–3.26 (m, 2H, CH_2N), 3.12 (d, 1H; J=17.2 Hz, CH2), 2.32 (ddd, 1H; J=6.0, 8.0, 14.1 Hz, CH_2CH_2N), 2.13 (ddd, 1H; J=6.7, 8.5, 14.1 Hz, CH_2CH_2N), 1.39 (s, 9H, CH_3); ^{13}C NMR (50 MHz, $CDCl_3$, 25 °C): δ=201.9, 169.4, 152.7, 136.4, 135.3, 127.7, 126.3, 124.7, 82.3, 59.7, 47.5, 37.1, 33.3, 27.7 (3C).

4.11. Synthesis of the cyclic β-amino esters 6a–f

Compounds **5a**–**f** were dissolved in MeOH and the reaction mixture was cooled to 0 °C with an ice bath. Then $NaBH_4$ (10 equiv) was carefully added in three portions during 1/2 h. After 1 h, the ice bath was removed and the reaction mixture was stirred overnight. Next 3 equiv of $NaBH_4$ were added and the reaction was stirred for additional 3 h. MeOH was partially removed under reduced pressure and the reaction was quenched with a 5% aqueous solution of NaOH. The mixture was transferred into a separatory funnel and extracted with CH_2Cl_2 (3×10 mL). The organic layers were dried over Na_2SO_4, filtered and concentrated under reduced pressure. Compounds **6a**–**f** were purified by column chromatography on deactivated silica gel. The enantiomeric excesses of the final β-amino esters were determined by HPLC analyses with chiral columns after Boc-protection of the amine group with di-*tert*-butyl dicarbonate. Racemic samples were prepared for HPLC analyses.

4.12. *tert*-Butyl (3a*R*,8b*S*)-2,3,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3a(1*H*)-carboxylate (6a)

This compound was obtained as a single diastereoisomer and isolated as an oil by column chromatography (elution gradient: hexane/ethyl acetate 90:10 to 60:40) in 55% yield and 98% ee as determined by HPLC analysis of the corresponding Boc-protected derivative [Lux cellulose-2, hexane/IPA 99:1, 0.8 mL/min, λ 230 nm, t (minor enantiomer)=10.2 min, t (major enantiomer)=10.6 min]. $[\alpha]_D^{27}$=−58.7 (c 1.0, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.45–7.38 (m, 1H, CH), 7.29–7.22 (m, 2H, CH), 7.21–7.16 (m, 1H, CH), 5.03 (s, 1H, CHN), 3.65 (d, 1H; J=16.9 Hz, CH_2), 3.16 (ddd, 1H; J=4.6, 7.6, 11.8 Hz, CH_2N), 3.05 (d, 1H; J=16.9 Hz, CH_2), 2.76 (td, 1H; J=7.6, 11.8 Hz, CH_2N), 2.75 (br s, 1H, NH), 2.42 (td, 1H; J=7.6, 13.0 Hz, CH_2CH_2N), 1.84 (ddd, 1H; J=4.6, 7.6, 13.0 Hz, CH_2CH_2N), 1.45 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=176.0, 141.9, 141.5, 128.2, 128.0, 125.2, 124.5, 80.9, 74.0, 60.3, 47.1, 41.8, 40.7, 28.0 (3C). FT-IR (KBr): ν 3205 (NH), 1722 (C=O) cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{21}NO_2$ $(M+H)^+$ 260.16451, found: 260.16473. *ent*-**6a**: 56% yield, 98% ee, $[\alpha]_D^{26}$=+56.6 (c 1.85, $CHCl_3$).

4.13. *tert*-Butyl (3a*R*,8b*S*)-7-chloro-2,3,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3a(1*H*)-carboxylate (6b)

This compound was obtained as a single diastereoisomer and isolated as an oil by column chromatography (elution gradient: hexane/ethyl acetate 90:10 to 70:30) in 57% yield and 94% ee as determined by HPLC analysis of the corresponding Boc-protected derivative [Chiralcel OD-H, hexane/IPA 98:2, 0.8 mL/min, λ 230 nm, t (major enantiomer)=6.4 min, t (minor enantiomer)=7.3 min]. $[\alpha]_D^{28}$=−58.5 (c 1.3, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.32 (s, 1H, CH), 7.20 (d, 1H, J=8.1 Hz, CH), 7.09 (d, 1H, J=8.1 Hz, CH), 4.98 (s, 1H, CHN), 3.58 (d, 1H; J=16.9 Hz, CH_2), 3.13 (ddd, 1H; J=4.2, 7.8, 11.6 Hz, CH_2N), 2.98 (d, 1H; J=16.9 Hz, CH_2), 2.68 (td, 1H; J=7.8, 11.6 Hz, CH_2N), 2.36 (td, 1H; J=7.8, 12.9 Hz, CH_2CH_2N), 2.3 (br s, 1H, NH), 1.81 (ddd, 1H; J=4.2, 7.8, 12.9 Hz, CH_2CH_2N), 1.45 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=175.8, 144.8, 139.8, 132.8, 128.2, 125.5, 125.3, 80.9, 74.0, 60.8, 47.3, 41.1, 41.0, 28.0 (3C). FT-IR (KBr): ν 3251 (NH), 1718 (C=O) cm^{-1}. HRMS (ESI): m/z calcd for $C_{16}H_{20}ClNO_2$ $(M+H)^+$ 294.12553, found: 294.12522. *ent*-**6b**: 72% yield, 93% ee, $[\alpha]_D^{22}$=+60.9 (c 1.25, $CHCl_3$).

4.14. *tert*-Butyl (4b*S*,7a*R*)-4b,6,7,8-tetrahydro[1,3]dioxolo [5,6]indeno[1,2-*b*]pyrrole-7a(5*H*)-carboxylate (6c)

This compound was obtained as a single diastereoisomer and isolated as an oil by column chromatography (elution: dichloromethane/methanol 95:5) in 50% yield and 96% ee as determined by HPLC analysis of the corresponding Boc-protected derivative [Chiralcel OD-H, hexane/IPA 98:2, 0.8 mL/min, λ 230 nm, t (major enantiomer)=7.8 min, t (minor enantiomer)=9.1 min]. $[\alpha]_D^{29}$=−61.9 (c 1.04, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=6.75 (s, 1H, CH), 6.57 (s, 1H, CH), 5.93–5.89 (m, 2H, CH_2O), 4.82 (s, 1H, CHN), 3.51 (d, 1H; J=16.6 Hz, CH_2), 3.08 (ddd, 1H; J=4.0, 7.5, 11.6 Hz, CH_2N), 2.88 (d, 1H; J=16.6 Hz, CH_2), 2.68 (td, 1H; J=7.5, 11.6 Hz, CH_2N), 2.32 (td, 1H; J=7.5, 12.8 Hz, CH_2CH_2N), 2.15 (br s, 1H, NH), 1.79 (ddd, 1H; J=4.0, 7.5, 12.8 Hz, CH_2CH_2N), 1.45 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=176.1, 148.0, 147.3, 135.3, 134.2, 105.0, 104.4, 101.0, 80.6, 74.1, 61.0, 47.1, 41.5, 41.4, 28.0 (3C). FT-IR (KBr): ν 3314 (NH), 1718 (C=O) cm^{-1}. HRMS (ESI): m/z calcd for $C_{17}H_{21}NO_4$ $(M+H)^+$ 304.15433, found: 304.15354.

4.15. *tert*-Butyl (3a*R*,8b*S*)-6,7-dimethoxy-2,3,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3a(1*H*)-carboxylate (6d)

This compound was obtained as a single diastereoisomer and isolated as an oil by column chromatography (elution: dichloromethane/methanol 95:5) in 44% yield calculated on the starting vinyl selenone **1** and 96% ee as determined by HPLC analysis of the corresponding Boc-protected derivative [Lux amylose-2, hexane/IPA 95:5, 1.0 mL/min, λ 230 nm, t (minor enantiomer)=28.1 min, t (major enantiomer)=31.1 min]. $[\alpha]_D^{34}$=−33.6 (c 0.91, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=6.84 (s, 1H, CH), 6.65 (s, 1H, CH), 4.90 (s, 1H, CHN), 3.87 (s, 3H,

OMe), 3.85 (s, 3H, OMe), 3.57 (d, 1H; J=16.5 Hz, CH_2), 3.10 (ddd, 1H; J=3.9, 8.0, 11.6 Hz, CH_2N), 2.93 (d, 1H; J=16.5 Hz, CH_2), 2.69 (ddd, 1H; J=7.0, 8.0, 11.6 Hz, CH_2N), 2.32 (td, 1H; J=8.0, 12.8 Hz, CH_2CH_2N), 2.18 (br s, 1H, NH), 1.80 (ddd, 1H; J=3.9, 7.0, 12.8 Hz, CH_2CH_2N), 1.47 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=176.2, 149.4, 148.8, 133.9, 133.0, 107.3, 106.9, 80.6, 74.7, 61.0, 55.9, 55.8, 47.3, 41.6, 41.5, 28.0 (3C). FT-IR (KBr): ν 3314 (NH), 1718 (C=O) cm^{-1}. HRMS (ESI): m/z calcd for $C_{18}H_{25}NO_4$ $(M+H)^+$ 320.18563, found: 320.18542.

4.16. *tert*-Butyl (3a*S*,4*S*,8b*S*)-4-phenyl-2,3,4,8b-tetrahydroindeno[1,2-*b*]pyrrole-3a(1*H*)-carboxylate (6e)

This compound was obtained as a single diastereoisomer and isolated as an oil by column chromatography (elution: dichloromethane/methanol 97:3) in 70% yield based on recovered starting material (35% of **5e** was recovered) and 95% ee as determined by HPLC analysis of the corresponding Boc-protected derivative [Lux cellulose-2, hexane/IPA 99:1, 1.0 mL/min, λ 230 nm, t (major enantiomer)=9.8 min, t (minor enantiomer)=13.9 min]. $[\alpha]_D^{21}$=+97.0 (c 0.85, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.38–7.32 (m, 1H, CH), 7.25–7.03 (m, 5H, CH), 6.97–6.86 (m, 3H, CH), 5.35 (s, 1H, CHN), 4.62 (s, 1H, CHPh), 2.96 (ddd, 1H; J=5.8, 7.4, 11.2 Hz, CH_2N), 2.66 (dt, 1H; J=7.4, 11.2 Hz, CH_2N), 2.37 (dt, 1H; J=7.4, 13.3 Hz, CH_2CH_2N), 2.10 (br s, 1H, NH), 1.94 (ddd, 1H; J=5.8, 7.4, 13.3 Hz, CH_2CH_2N), 0.97 (s, 9H, CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=173.6, 144.6, 143.4, 143.1, 128.8 (2C), 128.3, 128.2 (2C), 127.9, 126.5, 125.4, 125.1, 80.3, 70.2, 67.2, 59.9, 45.8, 41.1, 27.3 (3C). FT-IR (KBr): ν 3309, 1711 (C=O). HRMS (ESI): m/z calcd for $C_{22}H_{25}NO_2$ $(M+H)^+$ 336.19581, found: 336.19541.

4.17. *tert*-Butyl (3a*R*)-1,2,3,4,5,9b-hexahydro-3a*H*-benzo[*g*]indole-3a-carboxylate (6f)

This compound was obtained as a mixture of diastereoisomers (A:B=44:56) in 67% yield based on recovered starting material (40% of **5f** was recovered) and isolated by column chromatography (elution gradient: dichloromethane/methanol 98:2 to 95:5). ^{1}H NMR (400 MHz, $CDCl_3$, 25 °C): δ=7.47–7.43 (m, 1H, CH isomer A), 7.35–7.29 (m, 1H, CH isomer B), 7.20–7.08 (m, 6H, CH isomers A and B), 4.46 (s, 1H, CHN isomer A), 3.84 (s, 1H, CHN isomer B), 3.41–3.23 (m, 2H, CH_2N isomer B), 3.17–2.86 (m, 6H, CH_2N isomer A, CH_2 isomer B, NH isomers A and B), 2.77–2.70 (m, 2H, CH_2 isomer A), 2.65 (ddd, 1H, J=2.3, 8.7, 13.1 Hz, CH_2 isomer B), 2.33 (ddd, 1H; J=5.3, 8.5, 13.4 Hz, CH_2 isomer A), 2.22 (ddd, 1H; J=4.0, 8.6, 12.8 Hz, CH_2 isomer B), 2.18 (td, 1H; J=4.8, 13.4 Hz, CH_2 isomer A), 1.88 (td, 1H; J=7.5, 15.3 Hz, CH_2 isomer A), 1.1.84–1.66 (m, 3H, CH_2 isomer A, CH_2 isomer B); 1.42 (s, 9H, isomer A), 1.11 (s, 9H, isomer b); ^{13}C NMR (100 MHz, $CDCl_3$, 25 °C): δ=174.3, 165.6, 137.0, 136.6, 136.2, 130.0, 128.3, 128.1, 127.0, 126.5, 126.2, 125.6, 123.2, 80.7, 70.5, 68.4, 62.3, 58.8, 54.2, 46.6, 45.3, 38.8, 36.9, 29.8, 29.5, 27.9, 27.5, 27.3 (3C), 27.0 (3C). HRMS (ESI): m/z calcd for $C_{17}H_{23}NO_2$ $(M+H)^+$ 274.18015, found: 274.18026.

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