DOI: 10.1002/ejoc.201100996

A Combined Vinylogous Mannich/Diels–Alder Approach for the Stereoselective Synthesis of Highly Functionalized Hexahydroindoles

Bettina M. Ruff,[a] Sabilla Zhong,[a] Martin Nieger,[b] Marcel Sickert,[c] Christoph Schneider,[c] and Stefan Bräse*[a]

Keywords: Natural products / Nitrogen heterocycles / Cycloaddition / Stereoselective synthesis

A versatile strategy for the formation of hydroindole derivatives is reported. The molecules synthesized are highly functionalized and bear up to six stereogenic centers. We were able to develop a stereoselective route starting from nonchiral commercially available materials. Key steps in the formation of the bicyclic products are an organocatalytic vinylogous Mukaiyama–Mannich and a Diels–Alder reaction. The former uses a 1,1′-bi-2-napthol (BINOL)-based chiral Brønsted acid catalyst to build the first stereogenic center. The [4+2] cycloaddition proceeds highly diastereoselectively and furnishes one main stereoisomer, which represents the scaffold of the mycotoxins Rostratin B–D. Other transformations include iodolactonization, a Curtius rearrangement, additions, oxidations, and reductions.

Introduction

The indole moiety can be found in many natural products and pharmaceuticals. Partially or fully hydrogenated representatives of this class of hetero- and bicyclic compound can be *cis* or *trans* annelated. In addition, unsaturated derivatives can contain more stereogenic centers as they have various substituents. Because of the biological activity of many hydroindole substances, a versatile asymmetric strategy for their synthesis is needed. Nevertheless, only a few examples of the preparation of these structures are known in the literature. Wipf et al. have synthesized hexahydroindolinones starting from tyrosine or its derivatives.[1] Hexahydroindoles have been prepared by Bäckvall and Yeh using intramolecular 1,4-additions of amines to cyclic 1,3-dienes.[2] Hu, Wang et al. have employed a domino coupling/cyclization of 1,6-enynes with aryl halides for the synthesis of functionalized hexahydroindoles.[3] Oppolzer et al. reported the synthesis of octahydroquinolines and hexahydroindoles.[4] Their idea of using an intramolecular Diels–Alder reaction allows the application of linear precursors, building up at least two stereogenic centers in one cycloaddition step.

The mycotoxins Rostratin A–D (**1**–**4**) represent examples of thiodiketopiperazines (Figure 1), which consist of two identical octahydroindole amino acid moieties connected as a diketopiperazine and bridged with a disulfur unit. The Rostratins have been isolated from *Exserohilum rostratum* together with Exserohilone (**6**) and show in vitro cytotoxicity against the human colon carcinoma cell line HCT-116.[5] Exserohilone (**6**) and Epicorazin A (**7**) are examples of thiodiketopiperazines with a hexahydroindole moiety. Recently, Epicoccin R (**8**) has been isolated from the endophytic fungus *Epicoccum nigrum*.[6]

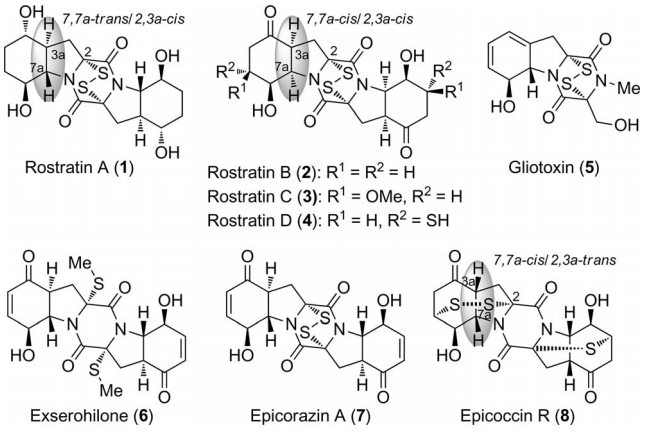


Figure 1. Structures of some mycotoxins with a thiodiketopiperazine core. Different ring-fusion possibilities are highlighted in gray.

Many other similar natural products containing a hydroindole moiety are known. However, only a few have been reached by total synthesis to date. The first was Gliotoxin (**5**) in 1981, which was also the first reported representative of this class of mycotoxins.[7] In the last few years, the total

[a] Institute of Organic Chemistry, Karlsruhe Institute of Technology (KIT),
Fritz-Haber-Weg 6, 76131 Karlsruhe, Germany
Fax: +49-721-698-48581
E-mail: braese@kit.edu
[b] Laboratory of Inorganic Chemistry, Department of Chemistry, University of Helsinki,
P. O. Box 55, 00014 University of Helsinki, Finland
[c] Institute of Organic Chemistry, University of Leipzig,
Johannisallee 29, 04103 Leipzig, Germany
E-mail: schneider@chemie.uni-leipzig.de
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100996.

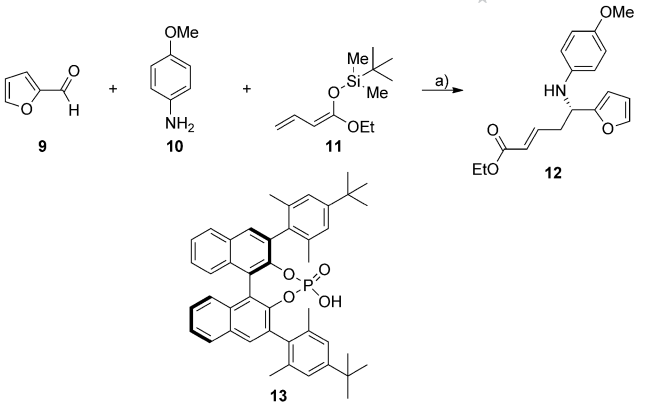
syntheses of Epicoccin G,[8] (+)-Gliocladine C,[9] and the dimeric pyrroloindole thiodiketopiperazines (+)-11,11′-Dideoxyverticillin A, (+)-Chaetocin A, (+)-Chaetocin C, and (+)-12,12′-Dideoxychetracin A have been successful.[10]

We have already reported a unified strategy to access the hydroindole building blocks needed for the total synthesis of the Epicoccins A, C, and D, Gliotoxin (**5**), Aranotins, Epicoccins (e.g. **8**), Exserohilone (**6**), Epicorazines (e.g. **7**), and Rostratin A (**1**).[11] This route, accomplishing the annelation of a second ring to a proline ring system by ring closing metathesis, gives 3a,7a-*cis*- and 3a,7a-*trans*-fused azabicyclic systems (for numbering and configuration see Figure 1). All of the synthesized *cis*-annelated substrates have a 2,3a-*trans* configuration. Using the strategy reported herein, with an intramolecular Diels–Alder reaction as the key step, we have developed access to 2,3a-*cis* configured azabicyclic structures. This is an important step towards the total synthesis of other interesting natural products, for example, the Rostratins B–D (**2**–**4**). Furthermore, it is important to develop a versatile strategy for the synthesis of analogues of biologically active secondary metabolites based on the mycotoxins shown in Figure 1. Modifications can lead to improved or more selective medicinal effects as well as better bioavailability and compliance in therapeutic applications.[12]

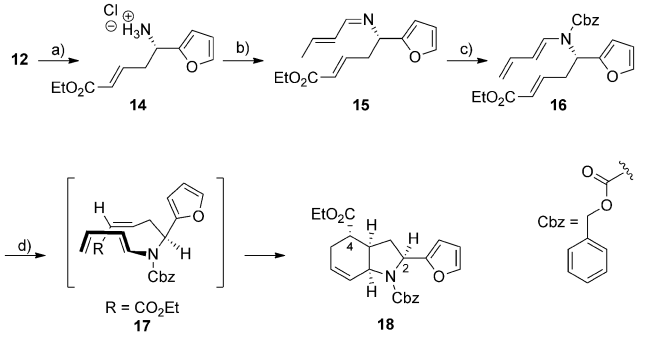
Results and Discussion

We were able to develop a strategy to synthesize hexahydroindoles with four stereogenic centers in six steps from commercially available starting materials. The δ-amino α,β-unsaturated carboxylic ester **12** was generated in a catalytic, enantioselective, vinylogous Mukaiyama–Mannich reaction. We have already developed and reported this asymmetric carbon–carbon bond-forming reaction of a silyldienolate and an imine with a BINOL-based phosphoric acid as a chiral catalyst.[13] For the purpose described here, we improved the three-component Mannich reaction consisting of 2-furfural (**9**), *p*-anisidine (**10**), and silyldienolate **11** with optimized solvent and temperature conditions for large-scale preparations (Scheme 1).

Hence, we were able to synthesize the unsaturated ester **12** in multigram quantities with an excellent yield and good enantioselectivity starting from commercially available **9** and **10**, and **11**, which is accessible quantitatively from ethyl but-3-enoate in one step.[14] The emerging, yet protected (the furan ring can be cleaved to a carboxylic acid, see below) amino acid **12** is *S* configured at the α-carbon atom and retains its stereochemical integrity throughout the synthetic process described here. The *p*-methoxyphenyl protecting group can be cleaved in very good yields with periodic acid to afford hydrochloride **14** (Scheme 2).[15] Deprotection with trichloroisocyanuric acid led to similar results. Although the use of ceric ammonium nitrate also led to deprotection, only decomposed material was observed after work up. However, if di-*tert*-butyldicarbonate was added in situ, the Boc-protected amine was isolated.[16]



Scheme 1. Large-scale application of the vinylogous Mukaiyama–Mannich reaction: a) 3 mol-% **13**, –55 °C, 2-Me-2-butanol/*t*BuOH/THF, 1:1:1 (c = 0.65), 0.25 equiv. H_2O, 95%, 81–89% *ee*. See also ref.[13]

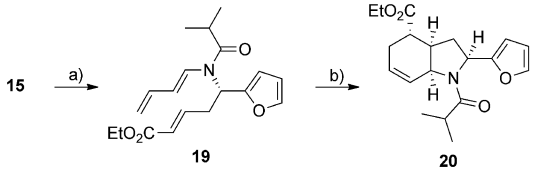


Scheme 2. Synthesis of the Diels–Alder substrate **16** and hexahydroindole **18**: a) H_5IO_6, 1 M H_2SO_4, MeCN/H_2O, 1:1, room temp., 95%; b) NEt_3, CH_2Cl_2, room temp.; molecular sieves 4 Å, Et_2O, crotonaldehyde, room temp.; c) benzylchloroformate, toluene, molecular sieves 4 Å, 0 °C → room temp., 65%, 81% *ee* (two steps); d) (*N*,*O*)-bis(trimethylsilyl)acetamide, *o*-xylene, 175 °C, 61%, 82% *ee*.

The following transformations were carried out according to our previously reported procedure for the synthesis of hexahydroindole carboxylic acids.[17] Hydrochloride **14** was converted into the free amine using triethylamine as a base. This was immediately condensed with crotonaldehyde to give imine **15**. The water-sensitive product is only stable for a few hours. A NMR spectrum measured directly showed clean product, whereas a spectrum recorded after a day showed nothing but decomposed material. Addition of benzylchloroformate with *N*,*N*-diethylaniline as a base afforded **16** in 65% yield in two steps. Compound **16** is the direct precursor of an intramolecular Diels–Alder reaction. Upon heating to 175 °C in a pressure tube with 1 equiv. (*N*,*O*)-bis(trimethylsilyl)acetamide as Lewis acid and *o*-xylene as solvent, **16** reacted by [4+2] cycloaddition to give **18** in 61% yield. This yield represents the isolated amount of the main stereoisomer with the two rings being *cis* annelated (*R*-C-3a and *S*-C-7a) and C-2 and C-4 in *S* configuration. A trace amount of a mixture of other diastereoisomers was also formed during the reaction, but we were unable to characterize it and assign the stereochemistry. The structure

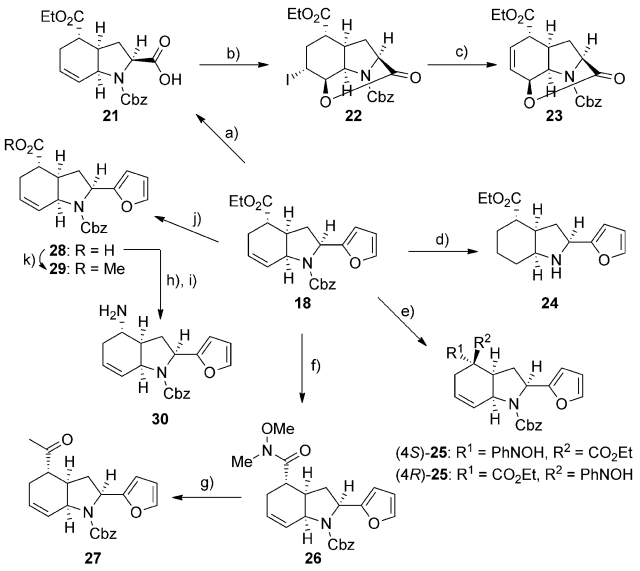
of **18** was unequivocally confirmed by the crystallographic analysis of **25** (see below). The chiral center at C-2 built in the vinylogous Mannich reaction in the first step induced the stereoselective formation of the other three stereogenic centers in the intramolecular Diels–Alder reaction. The dienophile attacks the diene in the *exo* position[18] in **17** (Scheme 2). This attack is favored here, but theoretical evaluation of the four possible diastereotopic transition states has not been performed. Overall, we achieved the synthesis of enantiomerically enriched hexahydroindole **18** – bearing four stereogenic centers – in only six steps and 36% yield from commercially available materials.

Instead of having carboxybenzyl (Cbz) as a protecting group, other substituents are possible at the indole nitrogen atom. To show this, we used isobutyryl chloride for the formation of Diels–Alder precursor **19** (Scheme 3). The cycloaddition of this substrate furnished indole derivative **20** in a similar overall yield (35%) to the Cbz-substituted **16**. The stereochemistry of **20** was confirmed by NOESY experiments as well as by analogy to **18**.



Scheme 3. Synthesis of hexahydroindole **20**: a) $(CH_3)_2CHCOCl$, NEt_3, DMAP, CH_2Cl_2, molecular sieves 4 Å, –78 °C → 0 °C, 79% (two steps); b) (*N*,*O*)-bis(trimethylsilyl)acetamide, *o*-xylene, 175 °C, 49%.

Hexahydroindole **18** was subjected to various transformations, which are summarized in Scheme 4. The furan ring represents an aldehyde moiety, which can be oxidatively cleaved with sodium dihydrogen phosphate, sodium chlorite, and hydrogen peroxide. The use of the furan ring as a protecting group for a carboxylic acid improved our previously reported strategy for the (racemic) synthesis of hexahydroindoles with two indistinguishable ester moieties (see ref.[17]). Acid **21** was treated with iodine and sodium hydrogen carbonate in an iodolactonization reaction. The attack occurs from the convex side of bicycle **21** to give the six-membered lactone **22**. This step enabled us to introduce an oxygen functionality to the more hindered side of hexahydroindole **18**. Other attempts, such as Sharpless[19] and Woodward[20] dihydroxylation or epoxidation with *m*CPBA, were unsuccessful and led to the isolation of starting materials or decomposition. Derivative **22** already contains all of the stereochemical information needed for the total synthesis of the Rostratins B–D (**2**–**5**). The iodine atom should be easily replaced by a methoxy group in a nucleophilic substitution, which would lead to the synthetically challenging scaffold of Rostratin C (**3**), with the substituents at C-5 and C-6 lying in the poorly accessible convex side of the bicyclic system. However, a first attempt to replace the iodine atom with methanol led to the formation of **23**, which nevertheless represents an interesting molecule. After the conditions for this reaction are optimized, **23** can be used as a precursor of Rostratin B (**2**) or D (**4**).



Scheme 4. Transformations of hexahydroindole **18**: a) $NaH_2PO_4 \times 2\ H_2O$, H_2O_2, $NaClO_2$, $MeCN/H_2O$ (6:1), 0 °C → reflux, 54%; b) I_2, $NaHCO_3$, CH_2Cl_2, 0 °C → room temp., 75%; c) *m*CPBA, MeOH, CH_2Cl_2, room temp., 41%, *rac*; d) H_2, 10% Pd/C, MeOH, room temp., 88%, *rac*; e) LiHMDS, THF, –78 °C → 0 °C; PhNO, –78 °C, 55%; f) *N*,*O*-dimethylhydroxylamine hydrochloride, *n*BuLi, THF, –78 °C → room temp.; then **18**, THF, –78 °C, 78%, *rac*; g) MeMgBr, THF, 0 °C, 82%; h) DPPA, NEt_3, *t*BuOH, reflux, 70%, *rac*; i) TFA, H_2O, CH_2Cl_2, room temp., 98%; j) LiOH, H_2O, THF, room temp., 99%; k) $TMSCHN_2$, Et_2O, MeOH, 0 °C → room temp., 74%, *rac*.

The convenience of Cbz as a protecting group was shown by its reductive cleavage with hydrogen and 10% palladium/charcoal. The free amine **24** – representing an octahydroindole derivative – was isolated in very good yields. If the reduction of the double bond is unwanted, it can be avoided by previous functionalization.

Addition of nitrosobenzene to the lithium enolate of **18**, generated in situ with lithium bis(trimethylsilyl)amide, yielded hydroxylamine **25**.[21] No diastereoselectivity was observed here and we obtained the epimers (4*S*)-**25** and (4*R*)-**25** in a 1:1 ratio. We were able to crystallize racemic[22] (4*S*)-**25** from dichloromethane and *n*-pentane, and its crystal structure is shown in Figure 2.

In the course of our work we focused on the modification of the C-4 ethyl ester moiety. Upon treatment with *N*,*O*-dimethylhydroxylamine hydrochloride and *n*-butyllithium we obtained Weinreb amide **26** in good yields. This amide was converted to methylketone **27** with methylmagnesium bromide in tetrahydrofuran (THF).

Cleavage of ethyl ester **18** with lithium hydroxide in water and THF furnished the free carboxylic acid **28** in quantitative yields, which was converted into the methyl ester **29** with trimethylsilyl diazomethane. Treatment of acid **28** with diphenylphosphoryl azide (DPPA) and triethylamine with heating gave carbamate **32**.[23] An initially built acyl azide is immediately converted into isocyanate **31** under the elimi-

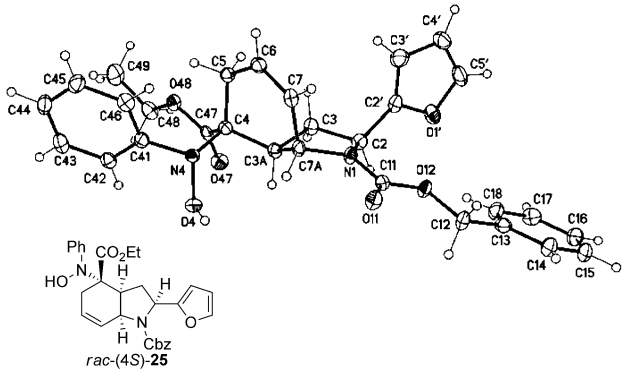
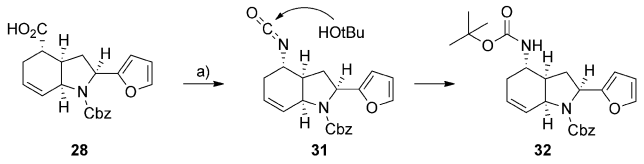


Figure 2. Molecular structure *rac*-(4*S*)-**25** (displacement parameters are drawn at 50% probability; disordered solvent omitted for clarity).

nation of nitrogen in a Curtius rearrangement (Scheme 5). Compound **31** is attacked by *tert*-butanol to give Boc-protected amine **32**, which can be deprotected with trifluoroacetic acid (TFA) to furnish the free amine **30**.



Scheme 5. Curtius rearrangement of acid **28** to give Boc-protected amine **32**: a) DPPA, NEt_3, reflux, 78%.

All of these modifications show the versatility of Diels–Alder product **18** and its potential to serve as a precursor in the total synthesis of natural products [e.g. Rostratins B–D (**2**–**4**)]. Rostratins are C_2 symmetrical thiodiketopiperazines with two octahydroindole moieties as monomers, which are similar to many molecules described in Scheme 4. The applicability of our earlier method to condense two amino acids to give diketopiperazines[24] for complex hydroindole systems has already been proven in previous studies in our group.[11]

Conclusions

We were able to combine vinylogous Mukaiyama–Mannich and Diels–Alder reactions to build hexahydroindoles **18** and **20** in only six steps in 36 and 35% yield, respectively. Both transformations were accomplished with excellent stereoselectivities. One of four stereogenic centers found in the bicyclic product is introduced using a chiral BINOL-based phosphoric acid as a catalyst in the Mannich reaction. This stereogenic information induces the configuration of three other stereogenic centers during the highly diastereoselective Diels–Alder reaction.

Furthermore, various highly functionalized hydroindoles can be synthesized using many different types of reactions. The derivatives described herein have not only a potential pharmaceutical benefit themselves, but also represent precursors of complex natural products.

Experimental Section

General: NMR spectra were recorded with Bruker AM 400, Bruker Avance 300 or Bruker DRX 500 spectrometer as solutions. Chemical shifts are expressed in ppm downfield from tetramethylsilane and are referenced to residual solvent peaks. All coupling constants are absolute values expressed in Hz. The descriptions of signals include: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. The spectra were analyzed according to the first order. The ^{13}C NMR signal structure was analyzed by DEPT and is described as follows: + = primary or tertiary C atom (positive signal), – = secondary C atom (negative signal) and q = quaternary C atom (no signal). MS (EI and FAB) were performed with a Finnigan MAT 90 (70 eV). IR spectra were recorded with a FT-IR Bruker IFS 88. Elemental analysis was performed with an Elementar Vario Microcube. Optical rotations were determined with a Perkin–Elmer 241 polarimeter at 20 °C with a glass cuvette and the D line of sodium. Solvents, reagents, and chemicals were purchased from Aldrich, Fluka, ABCR, and Acros. THF was distilled with sodium/potassium prior to use. Dichloromethane was distilled with calcium hydride. Toluene and diethyl ether were distilled with sodium. All reactions involving moisture-sensitive reactants were executed under an argon atmosphere using oven-dried glassware. All other solvents, reagents, and chemicals were used as purchased unless stated otherwise.

Ethyl (*S*,*E*)-5-(Furan-2-yl)-5-(4-methoxyphenylamino)pent-2-enoate (12): (gram scale procedure): A solution of *p*-anisidine (1.39 g, 11.2 mmol, 1.00) and **13** (225 mg, 337 μmol, 0.03 equiv.) in THF/*tert*-butanol/2-methylbutan-2-ol (1:1:1, *c* = 0.65 mol/L, 18 mL) and H_2O (0.25 equiv.) was stirred for 1 min at room temp. 2-Furfural (1.19 g, 12.4 mmol, 1.10 equiv.) was added and the mixture was stirred for 30 seconds at room temp. and for 5 min at –55 °C. Compound **11** (3.83 g, 16.8 mmol, 1.50 equiv.) was added over 10 min. The mixture was stirred for 6 h at –55 °C before silica gel (2 g) was added, and the mixture stirred for 10 min at room temp. The solvents were evaporated under reduced pressure and the residue was purified by column chromatography (diethyl ether/*n*-hexane, 1:5) to afford **12** (3.36 g, 10.7 mmol, 95%, 81–89% *ee*[13c]) as a yellow oil. R_f (cyclohexane/ethyl acetate, 5:1) = 0.32. $[\alpha]_D^{20}$ = –41.0 (*c* = 0.58, $CHCl_3$). HPLC conditions: AS-H chiralpak column; *n*-heptane/2-propanol = 90:10; 20 °C; flow rate = 0.7 mL/min; minor enantiomer t_R = 13.51 min; major enantiomer t_R = 16.39 min. For spectroscopic data see ref.[13b]

(*S*,*E*)-5-Ethoxy-1-(furan-2-yl)-5-oxopent-3-en-1-aminium Chloride (14): To a solution of **12** (523 mg, 1.49 mmol) in MeCN/H_2O (1:1, 38 mL) were added periodic acid (339 mg, 1.49 mmol) and 1 M aqueous sulfuric acid (2.28 mL). The mixture was stirred for 2 h at room temp. and then washed with dichloromethane (3 × 100 mL). The aqueous phase was brought to pH 10.5 by addition of 5 M aqueous KOH solution and extracted into ethyl acetate (3 × 100 mL). The combined organic phases were dried with sodium sulfate, acidified to pH 1 with HCl (1 M in ethyl acetate), and evaporated under reduced pressure to give **14** (347 mg, 95%) as a brown oil. $[\alpha]_D^{20}$ = +14.3 (*c* = 0.41, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.1 Hz, 3 H, CH_3), 2.99–3.07 (m, 2 H, $CH_2CH{=}CH$), 4.14 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.54–4.63 (m, 1 H, $CHNH_3$), 5.93 (d, ^3J = 15.5 Hz, 1 H, $CH_2CH{=}CH$), 6.31–6.35 (m, 1 H, H_{fur}), 6.52–6.57 (m, 1 H, H_{fur}), 6.68–6.79 (m, 1 H, $CH_2CH{=}CH$), 7.39–7.42 (m, 1 H, $O_{fur}CH{=}CHCH$), 8.82 (br. s, 3

H, NH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (+, CH_3), 34.2 (–, CH_2CH=CH), 48.1 (+, $CHNH_3$), 60.6 (–, CH_2CH_3), 110.4 (+, C_{fur}), 110.8 (+, C_{fur}), 128.8 (+, CH_2CH=CH), 140.8 (+, $O_{fur}CH$=CHCH), 143.6 (+, CH_2CH=CH), 148.0 (q, C_{fur}), 165.9 (q, C=O) ppm. IR (film): $\tilde{\nu}$ = 3417 (s), 2922 (s), 1714 (s), 1659 (m), 1505 (m), 1472 (m), 1184 (m), 1036 (m), 760 (m), 598 (w) cm^{-1}. MS (FAB, matrix: 3-NBA): *m*/*z* (%) = 210 (25) [M]$^+$, 193 (100), 154 (22), 136 (28), 119 (26), 109 (30). HRMS: calcd. for $C_{11}H_{16}NO_3$ [M – Cl]$^+$ 210.1125; found 210.1127. $C_{11}H_{16}ClNO_3$ (245.71): calcd. C 53.77, H 6.56, N 5.70; found C 53.05, H 6.58, N 6.19.

Ethyl (*S*,*E*)-5-[(*Z*)-{(*E*)-But-2-enylidene}amino]-5-(furan-2-yl)pent-2-enoate (15): To a solution of **14** (820 mg, 3.34 mmol) in dichloromethane (15 mL) was added Et_3N (463 µL, 3.34 mmol). The mixture was stirred for 2 h at room temp., filtered, and evaporated under reduced pressure (*T* = 20 °C). The residue was dissolved in diethyl ether (15 mL), filtered, and evaporated under reduced pressure (*T* = 20 °C). The resulting free amine was dissolved in diethyl ether over molecular sieves (4 Å) and treated drop wise with crotonaldehyde (304 µL, 3.67 mmol, 1.10 equiv.) at 0 °C. The mixture was brought to room temp., stirred for 15 h, filtered, and evaporated under reduced pressure (*T* = 20 °C) to give **15** as a brown oil. The hydrolysis-sensitive product was used immediately without purification in the next step. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.87 (d, ^3J = 5.2 Hz, 3 H, CH_3CH=CH), 2.75–2.95 (m, 2 H, CH_2CH=CH), 4.16 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.37 (t, ^3J = 7.0 Hz, 1 H, CH_2CHN), 5.87 (d, ^3J = 15.6 Hz, 1 H, CH_2CH=CH), 6.15–6.31 (m, 4 H, 2 × H_{fur}, CH_3CH=CH), 6.85 (dt, ^3J = 7.1, 15.6 Hz, 1 H, CH_2CH=CH), 7.34–7.36 (m, 1 H, $O_{fur}CH$=CHCH), 7.86 (d, ^3J = 8.0 Hz, 1 H, N=CH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 18.5 (+, CH_3CH=CH), 37.1 (–, CH_2CH=CH), 60.3 (–, CH_2CH_3), 66.1 (+, CH_2CHN), 106.6 (+, C_{fur}), 110.3 (+, C_{fur}), 116.6, 123.9, 130.9, 142.2, 144.6 (+, 5 × = CH), 154.0 (q, C_{fur}), 164.6 (+, N=CH), 166.4 (q, C=O) ppm. GC–MS: *m*/*z* = 261 [M]$^+$, 246, 216, 207, 188, 148, 130, 119.

Ethyl (*S*)-5-[(Benzyloxycarbonyl){(*E*)-buta-1,3-dienyl}amino]-5-(furan-2-yl)pent-2-enoate (16): *N*,*N*-diethylaniline (219 µL, 1.76 mmol, 1.50 equiv.) was added to a solution of benzylchloroformate (256 µL, 21.41 mmol, 1.20 equiv.) in toluene (10 mL) with molecular sieves (4 Å) at 0 °C. After 30 min, a solution of **15** (307 mg, 1.18 mmol) in toluene (10 mL) was added and the mixture was stirred for 2 d at room temp. It was filtered, washed with dichloromethane, and evaporated under reduced pressure. Column chromatography (cyclohexane/ethyl acetate, 10:1) afforded **16** (303 mg, 65% over 2 steps, 81% *ee*) as a yellow oil. $[\alpha]_D^{20}$ = –20.8 (*c* = 0.23, $CHCl_3$). R_f (cyclohexane/ethyl acetate, 10:1) = 0.25. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.94–3.10 (m, 2 H, CH_2CHN), 4.17 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.92 (d, $^3J_{cis}$ = 10.4 Hz, 1 H, CH_2=CH), 5.01 (d, $^3J_{trans}$ = 16.9 Hz, 1 H, CH_2=CH), 4.98–5.05 (m, 2 H, OCH_2Ph), 5.49–5.60 (m, 1 H, CH_2CHN), 5.77–5.93 (m, 2 H, =CH), 6.16–6.27 (m, 2 H, =CH), 6.31–6.35 (m, 1 H, =CH), 6.77 (d, ^3J = 14.4 Hz, 1 H, NCH=CH), 6.89 (dt, ^3J = 7.0, 15.3 Hz, 1 H, CH_2CH=CH), 7.30–7.40 (m, 6 H, 5 × H_{Ph}, $O_{fur}CH$=CHCH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 32.6 (–, CH_2CH=CH), 52.6 (+, CH_2CHN), 60.3 (–, CH_2CH_3), 68.3 (–, OCH_2Ph), 107.7 (+, C_{fur}), 110.4 (+, C_{fur}), 114.4 (–, CH_2=CH), 115.9, 124.3, 128.0, 128.3, 128.5, 129.1, 135.2 (+, 9 × =CH), 135.7 (q, C_{Ph}), 142.0, 143.3 (+, 2 × =CH), 151.8 (q, NC=O), 153.9 (q, C_{fur}), 166.0 (q, C=OOEt) ppm. IR (ATR): $\tilde{\nu}$ = 2938 (vw), 1698 (w), 1400 (vw), 1336 (vw), 1155 (vw), 1008 (vw), 731 (vw), 696 (vw) cm^{-1}. MS (FAB, matrix: 3-NBA): *m*/*z* (%) = 396 (8) [M + H]$^+$, 283 (8), 203 (9), 193 (28), 154 (18), 91 (100). HRMS: calcd. for $C_{23}H_{26}NO_5$ [M]$^+$ 396.1811; found 396.1807. HPLC conditions: OD chiralcel column; *n*-heptane/2-propanol = 95:5; 10 °C; flow rate = 0.7 mL/min; minor enantiomer t_R = 13.16 min; major enantiomer t_R = 14.59 min.

1-Benzyl 4-Ethyl (2*S*,3a*R*,4*S*,7a*S*)-2-(Furan-2-yl)-3,3a,4,5-tetrahydro-1*H*-indole-1,4(2*H*,7a*H*)-dicarboxylate (18): To a solution of **16** (383 mg, 969 µmol, 1.) was added (*N*,*O*)-bis(trimethylsilyl)acetamide (240 µL, 197 mg, 969 µmol). The mixture was heated in a vial at 175 °C for 7 d. It was evaporated under reduced pressure and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 10:1) to afford **18** (234 mg, 61%, 82% *ee*) as a yellow oil. R_f (cyclohexane/ethyl acetate, 5:1) = 0.24. $[\alpha]_D^{20}$ = +85.4 (*c* = 0.52, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$):[25] δ = 1.25 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.09–2.19, 2.22–2.42 [2 × m, 4 H, CH_2CH(COOEt)$CHCH_2$], 2.59–2.68 (m, 1 H, CHCOOEt), 2.75–2.87 (m, 1 H, CHCHCOOEt), 4.09–4.21 (m, 2 H, CH_2CH_3), 4.51–4.59 (m, 1 H, CH=CHCHN), 4.96 (t, ^3J = 7.6 Hz, 1 H, CHC$_{fur}$), 5.05–5.17 (m, 2 H, OCH_2Ph), 5.72–5.81 (m, 1 H, CH=CHCHN), 5.87–6.03 (m, 1 H, CH=CHCHN), 6.03–6.20 (m, 1 H, O_{fur}-CH=CHCH), 6.26–6.31 (m, 1 H, $O_{fur}CH$=CHCH), 7.27–7.40 (m, 6 H, 5 × H_{Ph}, $O_{fur}CH$=CHCH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$):[25] δ = 14.2 (+, CH_3), 23.6 (–, $CHCH_2CH$), 33.4 (–, $CHCH_2CH$), 36.9 (+, CHCHCOOEt), 39.6 (+, CHCHCOOEt), 54.5 (+, CHN), 55.0 (CHN), 60.7 (–, CH_2CH_3), 66.8 (–, CH_2OPh), 106.0 (+, $O_{fur}CH$=CHCH), 110.3 (+, $O_{fur}CH$=CHCH), 125.2, 126.8, 127.7, 127.8, 128.3 (+, 7 × = CH), 130.3 (q, C_{Ph}), 136.6 (q, C_{fur}), 141.2 (+, $O_{fur}CH$=CHCH), 155.1 (q, NC=O), 174.3 (q, CO-OEt) ppm. IR: $\tilde{\nu}$ = 3033 (w), 2979 (m), 1703 (vs), 1499 (s), 1447 (s), 1299 (s), 1108 (s), 1027 (m), 736 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 395 (8) [M]$^+$, 304 (64), 260 (44), 186 (10), 91 (100). HRMS: calcd. for $C_{23}H_{25}NO_5$ [M]$^+$ 395.1733; found 395.1736. $C_{23}H_{25}NO_5$ (395.17): calcd. C 69.86, H 6.37, N 3.54; found C 69.38, H 6.47, N 3.29. HPLC conditions: AS-H chiralpak column; *n*-heptane/2-propanol = 98:2; 10 °C; flow rate = 0.7 mL/min; major enantiomer t_R = 29.38 min; minor enantiomer t_R = 33.69 min.

Ethyl *rac*-(*E*)-5-[*N*-{(*E*)-Buta-1,3-dienyl}isobutyramido]-5-(furan-2-yl)pent-2-enoate (19): To a solution of isobutyryl chloride (69.5 µg, 68.4 µL, 653 µmol, 1.20 equiv.) in dichloromethane (5.0 mL) with molecular sieves (4 Å) were added Et_3N (15.1 µL, 109 µmol, 2.00 equiv.) and 4-*N*,*N*-dimethylaminopyridine (3.32 mg, 27.0 µmol, 0.05 equiv.) at –78 °C. A solution of **15** (142 mg, 544 µmol) in dichloromethane (5.0 mL) was added dropwise. The mixture was slowly brought to 0 °C with stirring overnight. It was filtered, washed with dichloromethane, and silica was added. The solvent was removed under reduced pressure, and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 5:1) to afford **19** (143 mg, 79% over 2 steps) as a yellow oil. R_f (cyclohexane/ethyl acetate, 10:1) = 0.19. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.11 [d, ^3J = 6.7 Hz, 6 H, $CH(CH_3)_2$], 1.25 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 2.86–2.93 [m, 3 H, CH_2CH=CH, CH-$(CH_3)_2$], 4.15 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 5.06 (d, $^3J_{cis}$ = 10.2 Hz, 1 H, CH_2=CH), 5.12 (d, $^3J_{trans}$ = 17.0 Hz, 1 H, CH_2=CH), 5.75–5.91, 6.18–6.35, 6.79–6.87 (3 × m, 8 H, CH_2CHN, 7 × =CH), 7.33–7.36 (m, 1 H, $O_{fur}CH$=CHCH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 19.2, 19.3 [+, $CH(CH_3)_2$], 31.7 [+, $CH(CH_3)_2$], 32.4 (–, CH_2CH=CH), 50.3 (+, CH_2CHN), 60.3 (–, CH_2CH_3), 107.8, 110.3 (2 × =CH), 117.4 (–, CH_2=CH), 124.1, 128.1, 133.9, 142.0, 143.6 (+, 6 × =CH), 152.3 (q, C_{fur}), 166.0 (q, C=OOEt), 177.0 (q, NC=O) ppm. IR (film): $\tilde{\nu}$ = 2976 (w), 2932 (w), 1719 (w), 1637 (w), 1469 (vw), 1389 (vw), 1315 (vw), 1269 (vw), 1012 (vw), 740 (vw) cm^{-1}. MS (EI): *m*/*z* (%) = 331 (20) [M]$^+$, 193 (73), 192 (11), 162 (58), 119 (49), 43 (100). HRMS: calcd. for $C_{19}H_{25}NO_4$ [M]$^+$ 331.1784; found 331.1785.

***rac*-Ethyl 2-(Furan-2-yl)-1-isobutyryl-2,3,3a,4,5,7a-hexahydro-1*H*-indole-4-carboxylate (20):** To a solution of **19** (56.3 mg, 170 μmol) in *o*-xylene (5.0 mL) was added (*N*,*O*)-bis(trimethylsilyl)acetamide (41.5 μL, 170 μmol). The mixture was heated in a vial at 175 °C for 7 d. It was evaporated under reduced pressure, and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 3:1) to afford **20** (27.6 mg, 49%) as a yellow oil. R_f (cyclohexane/ethyl acetate, 3:1) = 0.29. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.85–0.93, 1.07–1.17 [2×m, 6 H, CH(CH_3)$_2$], 1.24–1.30 (m, 3 H, CH_2CH_3), 2.10–2.88 [m, 7 H, CH_2CH(COOEt)CHCH_2, CH-(CH$_3$)$_2$], 4.09–4.24 (m, 2 H, CH_2CH$_3$), 4.58–4.79, 4.95–5.02, 5.08–5.17 (3×m, 2 H, CH=CHCHNCH), 5.65–5.81, 6.04–6.16, 6.23–6.36 (3×m, 4 H, 2×CHC$_{fur}$, CH=CHCHN), 7.27–7.38 (m, 1 H, O$_{fur}$CH=CHCH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (+, CH_2CH_3), 19.2 [+, CH(CH_3)$_2$], 24.2 (–, CH=CHCH_2), 31.9 [+, CHCHCOOEt or CHCHCOOEt or CH(CH$_3$)$_2$], 35.8 (–, CH_2CHCHCOOEt), 36.5, 40.0 [+, CHCHCOOEt or CHCHCOOEt or CH(CH$_3$)$_2$], 53.3 (+, CHN), 54.8 (CHN), 60.7 (–, CH_2CH$_3$), 106.1 (+, O$_{fur}$CH=CHCH), 110.5 (+, O$_{fur}$CH=CHCH), 125.2 (+, CH=CHCH$_2$), 126.6 (+, CH=CHCH$_2$), 141.8 (+, O$_{fur}$CH=CHCH), 155.9 (q, C_{fur}), 174.4 (q, C=OOEt), 174.3 (q, NC=O) ppm. IR: $\tilde{\nu}$ = 2976 (m), 2935 (m), 1729 (s), 1642 (s), 1472 (m), 1311 (m), 1181 (s), 1091 (m), 1028 (m), 738 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 331 (14) [M]$^+$, 179 (63), 164 (43), 146 (16), 110 (28), 55 (100). HRMS: calcd. for $C_{19}H_{25}NO_4$ [M]$^+$ 331.1784; found 331.1786. $C_{19}H_{25}NO_4$ (331.41): calcd. C 68.86, H 7.60, N 4.23; found C 68.61, H 7.64, N 4.19.

(2*S*,3a*R*,4*S*,7a*S*)-1-(Benzyloxycarbonyl)-4-(ethoxycarbonyl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-2-carboxylic Acid (21): To a solution of **18** (88.0 mg, 223 μmol) in MeCN/H_2O (6:1, 10.5 mL) at 0 °C were added NaH_2PO_4×2 H_2O (208 mg, 1.34 mmol, 6.00 equiv.), $NaClO_2$ (201 mg, 2.23 mmol, 10.0 equiv.), and hydrogen peroxide (35 wt.-% in H_2O, 90.0 μL, 834 μmol, 3.75 equiv.). The mixture was heated to reflux for 8 h, cooled to room temp., diluted with H_2O (5 mL), acidified (pH 2) with diluted aqueous hydrogen chloride solution, and extracted into dichloromethane (3×15 mL). The combined organic phases were dried with sodium sulfate and evaporated under reduced pressure. The residue was purified by column chromatography (dichloromethane/methanol, 98:2 + 0.5% acetic acid) to afford **21** (45.0 mg, 54%) as a colorless oil. R_f (CH_2Cl_2/MeOH, 98:2 + 0.5% AcOH) = 0.24. $[\alpha]_D^{20}$ = +61.4 (*c* = 0.50, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.94–2.48, 2.66–2.86 [2×m, 6 H, CH_2CH(COOEt)CHCH_2], 4.15 (q, ^3J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.40 (t, ^3J = 7.7 Hz, 1 H, CHCOOH), 4.53 (d, ^3J = 4.7 Hz, 1 H, CH=CHCHN), 5.10–5.21 (m, 2 H, OCH_2Ph), 5.63–6.04 (m, 2 H, CH=CH), 7.28–7.39 (m, 5 H, H$_{ar}$), 7.92 (br. s, 1 H, COOH) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1 (+, CH_3), 23.0 (–, CHCH_2CH), 31.1 (–, CHCH_2CH), 36.8 (+, CHCHCOOEt) 39.0 (+, CHCHCOOEt), 54.8 (+, =CHCHN), 58.5 (+, NCHCOOH), 60.9 (–, OCH_2Ph), 67.8 (–, CH_2CH$_3$), 125.5, 125.7, 128.0, 128.2, 128.5 (+, 7×=CH), 136.0 (q, C_{Ph}), 156.2 (q, NC=O), 174.0 (q, CHC=OOEt), 175.3 (q, CHCOOH) ppm. IR (ATR): $\tilde{\nu}$ = 2936 (w), 1701 (m), 1414 (m), 1157 (m), 1112 (m), 1025 (m), 734 (m), 696 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 373 (2) [M]$^+$, 328 (7), 284 (21), 238 (44), 194 (7), 120 (12), 91 (100). HRMS: calcd. for $C_{20}H_{23}NO_6$ [M]$^+$ 373.1525; found 373.1522.

4-Benzyl 6-Ethyl (3*S*,4a*R*,5*R*,6*S*,8*R*,8a*R*)-8-Iodo-2-oxohexahydro-2*H*-3,5-methanobenzo[*b*][1,4]oxazin-4,6(3*H*)-dicarboxylate (22): To a solution of **21** (49.7 mg, 133 μmol) in dichloromethane (2 mL) and saturated aqueous sodium hydrogen carbonate solution (2 mL) was added iodine (67.6 mg, 266 μmol, 2.00 equiv.) at 0 °C. The mixture was stirred for 4 h at room temp., diluted with H_2O (5 mL), extracted into dichloromethane (3×15 mL), dried with sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 3:1) to afford **22** (50.0 mg, 75%) as a yellow oil. R_f (cyclohexane/ethyl acetate, 3:1) = 0.30. $[\alpha]_D^{20}$ = –3.6 (*c* = 0.59, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (t, ^3J = 7.1 Hz, 3 H, CH_3), 1.59–1.64, 2.29–2.37, 2.44–2.54, 2.56–2.73 [4×m, 5 H, CH_2CH(COOEt)CHCH_2], 3.14–3.24 (m, 1 H, CHCHCOOEt), 4.21 (q, ^3J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.35–4.45 (m, 1 H, ICH), 4.63–4.73 (m, 1 H, CHC=O$_{lac}$), 4.89–4.95 (m, 1 H, CHCHN), 4.95–5.03 (m, 1 H, ICHCHO$_{lac}$) 5.13–5.25 (m, 2 H, OCH_2Ph), 7.31–7.41 (m, 5 H, H$_{ar}$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.0 (+, CH_2CH_3), 18.8 (+, ICH), 25.1 [–, CH_2CH(COOEt)CHCH_2], 29.7 (+, CHCHCOOEt), 40.6 (+, CHCHCOOEt), 50.2 (+, ICHCOCHN), 56.1 (+, CHC=O$_{lac}$), 61.6 (–, CH_2CH$_3$), 67.9 (–, OCH_2Ph), 80.9 (+, ICHCHO$_{lac}$), 128.1, 128.5, 128.7 (+, 5×C_{Ph}), 135.6 (q, C_{Ph}), 153.6 (q, CHC=O$_{lac}$), 167.6 (NC=O), 172.7 (CHC=OOEt) ppm. IR (film): $\tilde{\nu}$ = 2979 (m), 1763 (s), 1717 (vs), 1413 (s), 1351 (s), 1313 (s), 1292 (s), 1260 (s), 1214 (s), 1113 (s), 1026 (s), 994 (s), 911 (m), 734 (s), 699 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 499 (1), [M]$^+$, 372 (1), 328 (10), 284 (11), 120 (5), 118 (8), 91 (100). HRMS: calcd. for $C_{20}H_{22}INO_6$ [M]$^+$ 499.0492; found 499.0495.

4-Benzyl 6-Ethyl *rac*-(3*S*,4a*R*,5*R*,6*S*,8a*S*)-2-Oxo-4a,5,6,8a-tetrahydro-2*H*-3,5-methanobenzo[*b*][1,4]oxazine-4,6(3*H*)-dicarboxylate (23): To a solution of **22** (25.9 mg, 52.0 μmol) in methanol (2 mL) and dichloromethane (0.6 mL) was added *m*CPBA (70 wt.-%, 32.0 mg, 130 μmol, 2.50 equiv.). The mixture was stirred for 90 min at room temp. Ethyl acetate (20 mL) was added and the organic phase was washed with 5% sodium hydrogen carbonate solution (2×20 mL), dried with sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 3:1) to obtain **23** (8.00 mg, 22.0 μmol, 41%) as a yellow oil. R_f = 0.21 (cyclohexane/ethyl acetate, 3:1). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.47 (ddd, ^2J = 13.7, ^3J = 7.4, ^3J = 7.4 Hz, 1 H, 9-H$_A$), 2.59–2.72 (m, 1 H, 9-H$_B$), 2.76–2.96 (m, 1 H, 8a-H), 3.25–3.36 (m, 1 H, 6-H), 4.18 (q, ^3J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.55–4.74 (m, 2 H, 3-H, 4a-H), 4.78–5.06 (m, 1 H, 5-H), 5.09–5.24 (m, 2 H, OCH_2Ph), 5.99–6.10 (m, 2 H, 7-H, 8-H), 7.22–7.45 (m, 5 H, 5×H$_{Ph}$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.1 (+, CH_2CH_3), 32.7 (–, C-9), 33.6 (+, C-8a), 43.6 (+, C-6), 51.8, 56.3 (+, C-3, C-4a), 61.6 (–, CH_2CH$_3$), 67.9 (–, OCH_2Ph), 69.4 (+, C-5), 125.7, 127.2 (+, C-7, C-8), 128.1, 128.4, 128.6 (+, 5×C_{Ph}), 134.7, 135.7 (q, C_{Ph}, NC=O), 169.2, 171.3 (q, COOEt, C-2) ppm. IR (ATR): $\tilde{\nu}$ = 3306 (m), 2956 (m), 1759 (w), 1712 (m), 1636 (m), 1533 (w), 1462 (w), 1400 (m), 1359 (w), 1322 (w), 1301 (w), 1264 (m), 1215 (w), 1145 (w), 1096 (vw), 1026 (w), 951 (m), 849 (w), 751 (m), 697 (w), 525 (m) cm^{-1}. MS (FAB, 3-NBA): *m*/*z* (%) = 372 (4) [M + H]$^+$, 328 (7), 236 (3), 149 (30), 91 (100). HRMS: calcd. for $C_{20}H_{22}NO_6$ [M]$^+$ 372.1447; found 372.1446.

Ethyl *rac*-2-(Furan-2-yl)octahydro-1*H*-indole-4-carboxylate (24): To a solution of **18** (60.2 mg, 152 μmol) in methanol (2.0 mL) was added palladium/charcoal (10%, 0.81 mg, 7.6 μmol, 0.05 equiv.), and the mixture was stirred for 3 h at room temp. under a hydrogen atmosphere. It was filtered through Celite®, evaporated under reduced pressure, and the residue was purified by column chromatography (CH_2Cl_2/MeOH, 98:2 + 0.5% Et_3N) to afford **24** (34.8 mg, 88%) as a yellow oil. R_f (CH_2Cl_2/MeOH, 98:2 + 0.5% NEt_3) = 0.19. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.35–1.94, 2.24–2.32, 2.52–2.56 [3×m, 10 H, CH_2CH(COOEt)CHCH_2CH_2CH_2], 3.30–3.35 (m, 1 H, CH_2CH_2CHN), 4.13 (q, ^3J = 7.1 Hz, 2 H, CH_2CH$_3$), 4.27–4.32 (m, 1 H, CHC$_{fur}$), 6.19 (d, ^3J = 3.1 Hz, 1 H, O$_{fur}$CH=CHCH), 6.30

(dd, ^3J = 3.1, ^3J = 1.9 Hz, 1 H, $O_{fur}CH{=}CHCH$), 7.34–7.37 (m, 1 H, $O_{fur}CH{=}CHCH$) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.2 (+, CH_3), 19.8, 27.5, 28.3, 36.3 (4 × –, CH_2), 39.8, 44.8, 54.0, 57.6, (4 × +, CH), 60.2 (–, CH_2CH_3), 105.0 (+, $O_{fur}CH{=}CHCH$), 110.1 (+, $O_{fur}CH{=}CHCH$), 141.7 (+, $O_{fur}CH{=}CHCH$), 157.8 (q, C_{fur}), 176.2 (q, COOEt) ppm. IR: $\tilde{\nu}$ = 2934 (s), 1728 (s), 1452 (m), 1376 (m), 1238 (m), 1110 (m), 802 (w), 735 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 263 (39) $[M]^+$, 218 (13), 190 (72), 109 (19), 99 (100). HRMS: calcd. for $C_{15}H_{21}NO_3$ $[M]^+$ 263.1521; found 263.1523.

1-Benzyl 4-Ethyl (2*S*,3a*S*,7a*S*)-2-(Furan-2-yl)-4-[hydroxy(phenyl)-amino]-3,3a,4,5-tetrahydro-1*H*-indole-1,4(2*H*,7a*H*)-dicarboxylate as C-4 epimers (25): To a solution of **18** (273 mg, 691 μmol) in THF (20 mL) was added LiHMDS (1.00 M in THF, 1.04 mL, 1.04 mmol, 1.50 equiv.) at –78 °C, and the mixture was stirred for 15 min at this temperature and for 30 min at 0 °C. A solution of nitrosobenzene (118 mg, 1.11 mmol, 1.60 equiv.) in THF (15 mL) was added over 30 min at –78 °C. The solution was stirred at –78 °C for 3 h. Water (10 mL) was added and, after warming to room temp., the mixture was extracted into ethyl acetate (3 × 150 mL), washed with 0.5 M sodium hydroxide solution (2 × 80 mL) and brine (80 mL), dried with sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 5:1) to afford (4*S*)-**25**, which was recrystallized from cyclohexane to give a colorless solid (82.5 mg, 164 μmol). The isomer (4*R*)-**25** was obtained as a yellow oil (82.7 mg, 165 μmol). Furthermore, a fraction of a 1:1 mixture of both isomers (24.5 mg, 49 μmol) was afforded. The epimers were obtained in a total yield of 55%. (4*S*)-**25**: R_f = 0.31 (cyclohexane/ethyl acetate, 3:1). $[\alpha]_D^{20}$ = +58.7 (*c* = 1.24, $CHCl_3$). M.p. 146–147 °C. Ratio of inversion isomers = 0.57:0.43. ^1H NMR (400 MHz, $CDCl_3$): δ = 1.01–1.15 (m, 3 H, CH_2CH_3), 1.84–2.01 (m, 1 H, 3-H_A), 2.11–2.40 (m, 3 H, 3-H_B, 5-H_2), 3.25–3.43 (m, 1 H, 3a-H), 4.02–4.16 (m, 2 H, CH_2CH_3), 4.80–5.10 (m, 4 H, 2-H, 7a-H, OCH_2Ph), 5.56–5.64 (m, 1 H, 6-H), 5.74–5.93 (m, 2 H, 7-H, 3′-H), 6.14–6.20 (m, 1 H, 4′-H), 6.32–6.76 (br. s, 1 H, OH), 6.97–7.32 (m, 11 H, 10 × H_{Ph}, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.9 (+, CH_2CH_3), 26.9, 27.1 (–, C-5), 32.1, 33.6 (–, C-3), 39.4, 40.0 (+, C-3a), 54.1, 54.2, 56.5, 57.0 (+, C-2, C-7a), 60.5, 60.7 (–, CH_2CH_3), 66.8 (–, OCH_2Ph), 70.7, 70.9 (q, C-4), 105.6, 106.5 (+, C-3′), 110.0 (+, C-4′), 122.4 (+, C-6), 123.7, 123.9, 125.4, 125.6, 127.5, 127.6, 127.7, 128.0, 128.3 (+, 10 × C_{Ph}), 127.2, 127.3 (+, C-7), 136.1, 136.5 (q, CH_2C_{Ph}), 140.9, 141.1 (+, C-5′), 148.3, 148.7, 154.2, 154.8, 155.0, 155.4 (q, NC_{Ph}, C-2′, NCOOBn), 171.0, 171.1 (q, COOEt) ppm. IR (ATR): $\tilde{\nu}$ = 3304 (w), 2982 (vw), 1732 (w), 1662 (m), 1465 (w), 1422 (m), 1356 (m), 1234 (m), 1190 (w), 1168 (w), 1142 (w), 1078 (w), 1065 (w), 1034 (w), 1011 (w), 967 (w), 940 (w), 890 (w), 879 (w), 838 (w), 818 (w), 795 (w), 746 (m), 733 (m), 701 (m), 677 (m), 601 (w), 563 (w), 539 (w), 505 (w) cm^{-1}. MS (EI): *m*/*z* (%) = 502 (2) $[M]^+$, 486 (3), 413 (4), 393 (45), 349 (7), 302 (4), 276 (6), 258 (10), 234 (7), 212 (14), 184 (13), 118 (8), 109 (26), 91 (100). HRMS: calcd. for $C_{29}H_{30}N_2O_6$ $[M]^+$ 502.2104; found 502.2107. $C_{29}H_{30}N_2O_6$ (502.57): calcd. C 69.31, H 6.02, N 5.57; found C 68.72, H 5.89, N 5.34. (4*R*)-**25**: R_f = 0.24 (cyclohexane/ethyl acetate, 3:1). Ratio of inversion isomers = 0.65:0.35. $[\alpha]_D^{20}$ = +94.1 (*c* = 0.83, $CHCl_3$). ^1H NMR (400 MHz, $CDCl_3$): δ = 1.11–1.29 (m, 3 H, CH_2CH_3), 1.95–2.08 (m, 1 H, 3-H_A), 2.18–2.48, 2.54–2.67, (2 × m, 3 H, 3-H_B, 5-H_2), 3.27–3.44 (m, 1 H, 3a-H), 4.10–4.18 (m, 2 H, CH_2CH_3), 4.61–4.71, 4.84–4.96 (2 × m, 1 H, 7a-H), 4.90–5.18 (m, 3 H, 2-H, OCH_2Ph), 5.57–5.71 (m, 1 H, 6-H), 5.73–5.99 (m, 1 H, 7-H), 6.04–6.31 (m, 2 H, 3′-H, 4′-H), 7.06–7.42 (m, 11 H, 10 × H_{Ph}, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.7, 13.8 (+, CH_2CH_3), 28.2, 28.7 (–, C-5), 32.2, 33.7 (–, C-3), 39.1, 39.4 (+, C-3a), 53.8, 54.0 (+, C-2), 56.7, 57.1 (+, C-7a), 60.9, 61.0 (–, CH_2CH_3), 66.6 (–, OCH_2Ph), 70.7, 70.9 (q, C-4), 105.5, 106.3 (+, C-3′), 110.0, 110.1 (+, C-4′), 122.8, 122.9 (+, C-6), 123.4, 125.9, 127.4, 127.5, 127.6, 127.8, 128.0, 128.2, 128.6, (+, 10 × C_{Ph}), 126.5, 126.5 (+, C-7), 136.2, 136.5 (q, CH_2C_{Ph}), 140.9, 141.1 (+, C-5′), 148.1, 154.4, 154.6, 154.7, 155.6 (q, NC_{Ph}, C-2′, NCOOBn), 170.9, 171.0 (q, COOEt) ppm. IR (ATR): $\tilde{\nu}$ = 3367 (vw), 2922 (vw), 1698 (w), 1595 (vw), 1487 (vw), 1451 (w), 1407 (w), 1353 (w), 1289 (w), 1239 (w), 1148 (w), 1109 (w), 1010 (w), 931 (vw), 884 (vw), 765 (w), 734 (w), 696 (m) cm^{-1}. MS (EI): *m*/*z* (%) = 502 (7) $[M]^+$, 486 (4), 413 (4), 393 (26), 320 (26), 276 (15), 266 (11), 234 (6), 212 (13), 184 (12), 118 (13), 109 (18), 91 (100). HRMS: calcd. for $C_{29}H_{30}N_2O_6$ $[M]^+$ 502.2104; found 502.2107. $C_{29}H_{30}N_2O_6$ (502.57): calcd. C 69.31, H 6.02, N 5.57; found C 68.72, H 5.89, N 5.34.

Benzyl 2*rac*-(2*S*,3a*R*,4*S*,7a*S*)--(Furan-2-yl)-4-[methoxy(methyl)carb-amoyl]-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (26): To a suspension of *N*,*O*-dimethylhydroxylamine hydrochloride (209 mg, 2.14 mmol, 4.50 equiv.) in THF (5 mL) was added a 2.5 M *n*-butyllithium solution (1.71 mL, 4.28 mmol, 9.00 equiv.) at –78 °C. The solution was stirred for 20 min at room temp. before cooling to –78 °C. A solution of **18** (188 mg, 476 μmol) in THF (5 mL) was added and the resulting mixture was stirred for another 2 h at –78 °C. Saturated aqueous ammonium chloride solution (10 mL) and water (5 mL) were added, and the mixture was extracted into ethyl acetate (3 × 30 mL), dried with sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 3:2) to afford **26** (153 mg, 372 μmol, 78%) as a colorless oil. R_f = 0.23 (cyclohexane/ethyl acetate, 1:1). ^1H NMR (500 MHz, $CDCl_3$): δ = 1.98–2.04 (m, 2 H, 3-H_A, 5-H_A), 2.19–2.23 (m, 1 H, 5-H_B), 2.39 (ddd, ^2J = 13.6, ^3J = 8.4, ^3J = 8.4 Hz, 1 H, 3-H_B), 2.78–2.84 (m, 1 H, 3a-H), 2.82–2.90 (m, 1 H, 4-H), 3.13 (s, 3 H, NCH_3), 3.38 (s, 3 H, OCH_3), 4.50–4.55 (m, 1 H, 7a-H), 5.05 (dd, ^3J = 8.4, ^3J = 3.4 Hz, 1 H, 2-H), 5.13 (s, 2 H, OCH_2Ph), 5.81–5.86 (m, 1 H, 6-H), 6.06–6.11 (m, 1 H, 3′-H), 6.09–6.25 (m, 1 H, 7-H), 6.26 (dd, ^3J = 3.1, ^3J = 1.8 Hz, 1 H, 4′-H), 7.23–7.35 (m, 6 H, 5 × H_{Ph}, 5′-H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 25.9 (–, C-5), 32.2 (+, NCH_3), 34.8 (–, C-3), 37.2, 37.4 (+, C-3a, C-4), 55.2 (+, C-2), 55.5 (+, C-7a), 61.4 (+, OCH_3), 66.9 (–, OCH_2Ph), 105.9 (+, C-3′), 110.3 (+, C-4′), 126.3, 126.6 (+, C-6, C-7), 127.7, 127.8, 128.4 (+, 5 × C_{Ph}), 136.6 (q, C_{Ph}), 141.2 (+, C-5′), 155.2, 156.1 (q, C-2′, NCOOBn), 175.6 [q, C(=O)-N(OCH_3)CH_3] ppm. IR (film): $\tilde{\nu}$ = 3114 (vw), 3033 (w), 3936 (w), 2246 (vw), 1701 (s), 1669 (s), 1498 (w), 1444 (m), 1408 (w), 1354 (s), 1320 (m), 1299 (m), 1174 (m), 1110 (m), 1077 (w), 1007 (m), 911 (w), 855 (w), 807 (vw), 770 (w), 734 (m), 698 (m), 599 (w), 469 (vw), 436 (vw) cm^{-1}. MS (EI): *m*/*z* (%) = 410 (10) $[M]^+$, 379 (4), 322 (13), 319 (17), 275 (28), 91 (58), 84 (100). HRMS: calcd. for $C_{23}H_{26}N_2O_5$ $[M]^+$ 410.1842; found 410.1845.

Benzyl *rac*-(2*S*,3a*R*,4*S*,7a*S*)-4-Acetyl-2-(furan-2-yl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (27): To a solution of **26** (35.8 mg, 87 μmol) in THF (2.5 mL) at 0 °C was added methylmagnesium bromide (3 M in THF, 145 μL, 436 μmol, 5.00 equiv.), and solution was stirred at this temperature for 30 min. Saturated ammonium chloride solution (1 mL) was added and the mixture was diluted with water (2 mL), extracted into ethyl acetate (3 × 10 mL), dried with sodium sulfate, and evaporated under reduced pressure. The residue was purified by column chromatography (cyclohexane/ethyl acetate, 3:1), which gave **27** (26.1 mg, 73 μmol, 82%) as a colorless oil. R_f = 0.19 (cyclohexane/ethyl acetate, 3:1). ^1H NMR (400 MHz, $CDCl_3$): δ = 2.06–2.16, 2.28–2.35 (2 × m, 2 H, 3-H_2), 2.11 (s, 3 H, CH_3), 2.16–2.28 (m, 2 H, 5-H_2), 2.62–2.69 (m, 1 H, 4-H), 2.71–2.78 (m, 1 H, 3a-H), 4.48–4.50 (m, 1 H, 7a-H), 4.97 (t, ^3J = 7.2 Hz, 1 H, 2-H), 5.11 (s, 2 H, OCH_2Ph), 5.73–5.80 (m, 1 H, 6-H), 5.91–6.05 (m, 1 H, 7-H), 6.07–6.16 (m, 1 H, 3′-H), 6.29 (dd,

^3J = 3.0, ^3J = 1.8 Hz, 1 H, 4′-H), 7.26–7.35 (m, 6 H, 5 × H_{Ph}, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9 (–, C-5), 28.8 (+, CH_3), 34.5 (–, C-3), 36.5 (+, C-3a), 47.2 (+, C-4), 54.4 (+, C-2), 55.1 (+, C-7a), 66.9 (–, OCH_2Ph), 106.1 (+, C-3′), 110.4 (+, C-4′), 125.1 (+, C-6), 127.1 (+, C-7), 127.8, 127.8, 128.4 (+, 5 × C_{Ph}), 136.6 (q, C_{Ph}), 141.1 (+, C-5′), 155.2, 155.5 (q, NC=O, C-2′), 210.0 (q, COMe) ppm. IR (film): $\tilde{\nu}$ = 3032 (w), 2946 (w), 1703 (vs), 1499 (w), 1446 (m), 1354 (s), 1297 (s), 1242 (m), 1173 (m), 1153 (m), 1107 (s), 1009 (m), 932 (w), 864 (w), 808 (w), 770 (m), 738 (m), 698 (w), 599 (w), 462 (vw) cm^{-1}. MS (EI): m/z (%) = 365 (6) $[M]^+$, 274 (100), 230 (14), 172 (14), 91 (66). HRMS: calcd. for $C_{22}H_{23}NO_4$ $[M]^+$ 365.1627; found 365.1629.

(2*S*,3a*R*,4*S*,7a*S*)-1-[(Benzyloxy)carbonyl]-2-(furan-2-yl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-4-carboxylic Acid (28): To a solution of **18** (155 mg, 392 μmol) in THF (6.5 mL) was added a solution of lithium hydroxide (93.9 mg, 3.92 mmol, 10.0 equiv.) in water (6.5 mL), and the mixture was stirred for 19 h at room temp. THF was evaporated under reduced pressure and the remaining aqueous solution was brought to pH 1 by addition of 1 M HCl. The mixture was extracted into ethyl acetate (3 × 30 mL), dried with sodium sulfate, and evaporated under reduced pressure to give **28** (144 mg, 392 μmol, 99%) as a slightly brown oil. R_f = 0.33 (CH_2Cl_2/MeOH, 20:1 + 0.5% acetic acid). $[\alpha]_D^{20}$ = +70.1 (c = 0.80, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12–2.20 (m, 1 H, 3-H_A), 2.28–2.44 (m, 3 H, 3-H_B, 5-H_2), 2.68–2.74 (m, 1 H, 4-H), 2.79–2.86 (m, 1 H, 3a-H), 4.56–4.62 (m, 1 H, 7a-H), 4.97 (t, ^3J = 7.6 Hz, 1 H, 2-H), 5.10 (s, 2 H, OCH_2Ph), 5.73–5.79 (m, 1 H, 6-H), 5.85–6.00 (m, 1 H, 7-H), 6.05–6.20 (m, 1 H, 3′-H), 6.28 (dd, ^3J = 2.7, ^3J = 1.9 Hz, 1 H, 4′-H), 7.10–7.41 (m, 6 H, 5 × H_{Ph}, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.3 (–, C-5), 34.4 (–, C-3), 36.5 (+, C-3a), 39.4 (+, C-4), 54.5 (+, C-2), 54.9 (+, C-7a), 67.0 (–, OCH_2Ph), 106.1 (+, C-3′), 110.3 (+, C-4′), 124.9 (+, C-6), 126.8 (+, C-7), 127.8, 127.9, 128.3 (+, 5 × C_{Ph}), 136.5 (q, C_{Ph}), 141.3 (+, C-5′), 155.2 (q, C-2′, NC=O), 179.9 (q, CO$_2$H) ppm. IR (film): $\tilde{\nu}$ = 3032 (w), 2950 (w), 1697 (s), 1499 (w), 1406 (m), 1354 (m), 1297 (m), 1175 (m), 1153 (m), 1108 (m), 1076 (m), 1009 (m), 930 (w), 885 (w), 807 (w), 732 (s), 695 (m), 598 (m), 461 (w) cm^{-1}. MS (FAB, 3-NBA): m/z (%) = 391 (42) $[M + H + Na]^+$, 368 (46) $[M + H]^+$, 324 (6), 323 (6), 276 (27), 232 (12), 210 (38), 91 (100). HRMS: calcd. for $C_{21}H_{22}NO_5$ $[M]^+$ 368.1498; found 368.1495.

1-Benzyl *rac*-(2*S*,3a*R*,4*S*,7a*S*)-4-Methyl-2-(furan-2-yl)-3,3a,4,5-tetrahydro-1*H*-indole-1,4(2*H*,7a*H*)-dicarboxylate (29): To a solution of **28** (45.6 mg, 124 μmol) in diethyl ether (2.2 mL) and methanol (0.22 mL) was added a 2 M trimethylsilyldiazomethane solution in diethyl ether (0.22 mL, 424 mmol, 3.50 equiv.) at 0 °C. The mixture was stirred for 1 h at 0 °C and 1 h at room temp. The solvent was evaporated under reduced pressure at 20 °C, and the residue was purified by column chromatography (cyclohexane/ethyl acetate, 5:1) to obtain **29** (35.1 mg, 92.0 μmol, 74%) as a colorless oil. R_f = 0.26 (cyclohexane/ethyl acetate, 3:1). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09–2.17, 2.22–2.42 (2 × m, 4 H, 3-H_2, 5-H_2), 2.62–2.74 (m, 1 H, 4-H), 2.78–2.85 (m, 1 H, 3a-H), 3.69 (s, 3 H, CH_3), 4.52–4.70 (m, 1 H, 7a-H), 4.96 (t, ^3J = 7.6 Hz, 1 H, 2-H), 5.10 (s, 2 H, OCH_2Ph), 5.72–5.81 (m, 1 H, 6-H), 5.83–6.03 (m, 1 H, 7-H), 6.05–6.23 (m, 1 H, 3′-H), 6.24–6.36 (m, 1 H, 4′-H), 7.20–7.44 (m, 6 H, 5 × H_{Ph}, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.6 (–, C-5), 34.8 (–, C-3), 36.9 (+, C-3a), 39.6 (+, C-4), 52.0 (+, CH_3), 54.5 (+, C-2), 55.0 (+, C-7a), 66.9 (–, OCH_2Ph), 106.0 (+, C-3′), 110.3 (+, C-4′), 125.0 (+, C-6), 126.9 (+, C-7), 127.8, 128.4 (+, 5 × C_{Ph}), 136.6 (q, C_{Ph}), 141.2 (+, C-5′), 155.1 (q, C-2′, NC=O), 174.8 (q, CO$_2$Me) ppm. IR (film): $\tilde{\nu}$ = 3032 (vw), 2950 (w), 1731 (m), 1697 (s), 1498 (vw), 1438 (w), 1404 (m), 1352 (m), 1297 (m), 1172 (m), 1153 (m), 1103 (m), 1077 (m), 1010 (m), 993 (m), 931 (w), 885 (w), 807 (w), 769 (w), 732 (m), 696 (m), 598 (w), 574 (vw), 458 (w) cm^{-1}. MS (EI): m/z (%) = 381 (6) $[M]^+$, 350 (5), 336 (6), 304 (5), 290 (100), 264 (9), 246 (59), 149 (30), 91 (69). HRMS: calcd. for $C_{22}H_{23}NO_5$ $[M]^+$ 381.1576; found 381.1572.

Benzyl (2*S*,3a*R*,4*S*,7a*S*)-4-Amino-2-(furan-2-yl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (30): To a solution of **32** (113 mg, 257 μmol) in dichloromethane (1.2 mL) were added water (40 μL) and TFA (410 μL, 610 mg, 5.30 mmol, 21.0 equiv.), and the mixture was stirred for 45 min at room temp. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (20 mL). The resulting solution was brought to pH 8 by addition of Et_3N, washed with saturated sodium hydrogen carbonate solution (15 mL), dried with sodium sulfate, and evaporated under reduced pressure. Compound **30** (85.2 mg, 252 μmol, 98%) was obtained as a slightly brown oil. R_f = 0.25 (CH_2Cl_2/MeOH, 10:1). $[\alpha]_D^{20}$ = +82.0 (c = 1.19, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.92–2.40 (m, 5 H, 3-H_2, 3a-H, 5-H_2), 3.05–3.35 (m, 1 H, 4-H), 4.51–4.69 (m, 1 H, 7a-H), 4.94 (t, ^3J = 7.6 Hz, 1 H, 2-H), 4.99–5.20 (m, 2 H, OCH_2Ph), 5.57–5.73 (m, 1 H, 6-H), 5.76–6.20 (m, 2 H, 7-H, 3′-H), 6.25–6.30 (m, 1 H, 4′-H), 7.08–7.38 (m, 6 H, 5 × H_{Ph}, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.9 (–, C-5), 33.8 (–, C-3), 43.3 (+, C-3a), 46.3 (+, C-4), 54.6 (+, C-2), 55.0 (+, C-7a), 66.9 (–, OCH_2Ph), 105.6 (+, C-3′), 110.3 (+, C-4′), 124.1 (+, C-6), 126.5 (+, C-7), 127.7, 127.8, 128.3 (+, 5 × C_{Ph}), 136.5 (q, C_{Ph}), 141.1 (+, C-5′), 155.1, 155.7 (q, NC=O, C-2′) ppm. IR (film): $\tilde{\nu}$ = 3366 (w), 3032 (w), 2906 (m), 1699 (s), 1587 (w), 1499 (w), 1451 (m), 1410 (s), 1354 (s), 1299 (m), 1213 (w), 1177 (m), 1153 (m), 1112 (s), 1010 (m), 992 (m), 930 (w), 874 (w), 808 (w), 770 (m), 735 (m), 698 (m), 600 (w), 478 (vw) cm^{-1}. MS (FAB, 3-NBA): m/z (%) = 339 (42) $[M + H]^+$, 278 (4), 247 (3), 231 (5), 203 (5), 186 (10), 91 (100). HRMS: calcd. for $C_{20}H_{23}N_2O_3$ $[M + H]^+$ 339.1709; found 339.1707.

Benzyl (2*S*,3a*R*,4*S*,7a*S*)-4-[(*tert*-Butoxycarbonyl)amino]-2-(furan-2-yl)-2,3,3a,4,5,7a-hexahydro-1*H*-indole-1-carboxylate (32): To a solution of **28** (210 mg, 572 μmol) in *tert*-butanol (8 mL) were added DPPA (250 μL, 320 mg, 1.10 mmol, 2.00 equiv.) and Et_3N (96.0 μL, 70.0 mg, 690 μmol, 1.20 equiv.). The mixture was heated to reflux for 4 h and stirred overnight at room temp. Water (10 mL) was added, and the aqueous phase was extracted into ethyl acetate (3 × 60 mL). The combined organic phases were dried with sodium sulfate, evaporated under reduced pressure, and purified by column chromatography (cyclohexane/ethyl acetate, 5:1) to give **32** (175 mg, 400 μmol, 78%) as a slightly yellow oil. R_f = 0.37 (cyclohexane/ethyl acetate, 3:1). $[\alpha]_D^{20}$ = +49.3 (c = 0.96, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.44 [s, 9 H, C(CH_3)$_3$], 1.96–2.08, 2.29–2.36, 2.41–2.46 (3 × m, 4 H, 3-H_2, 5-H_2), 2.56–2.79 (m, 1 H, 3a-H), 3.90–4.09 (m, 1 H, 4-H), 4.43–4.63 (m, 1 H, 7a-H), 4.75–4.84 (m, 1 H, NHBoc), 4.85–4.95 (m, 1 H, 2-H), 5.07 (s, 2 H, OCH_2Ph), 5.65–5.72 (m, 1 H, 6-H), 5.82–5.98 (m, 1 H, 7-H), 5.99–6.23 (m, 1 H, 3′-H), 6.24–6.30 (m, 1 H, 4′-H), 7.05–7.20, 7.20–7.45 (2 × m, 6 H, 5 × H_{Ph}, 5′-H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.7 (–, C-5), 28.4 [+, C(CH_3)$_3$], 34.0 (–, C-3), 39.9 (+, C-3a), 45.7 (+, C-4), 54.6 (+, C-2, C-7a), 66.9 (–, OCH_2Ph), 79.5 [q, C(CH$_3$)$_3$], 105.9 (+, C-3′), 110.2 (+, C-4′), 123.6, 127.2 (+, C-6, C-7), 127.7, 127.8, 128.3 (+, 5 × C_{Ph}), 136.5 (q, C_{Ph}), 141.2 (+, C-5′), 155.2 (q, 2 × NC=O, C-2′) ppm. IR (film): $\tilde{\nu}$ = 3331 (vw), 3114 (vw), 3032 (vw), 2975 (w), 2930 (w), 1695 (w), 1499 (w), 1454 (w), 1408 (w), 1353 (w), 1302 (w), 1245 (w), 1169 (w), 1110 (w), 1052 (w), 1009 (vw), 932 (vw), 876 (vw), 805 (vw), 770 (vw), 732 (w), 697 (vw), 599 (vw), 462 (vw) cm^{-1}. MS (EI): m/z (%) = 438 (16) $[M]^+$, 381 (21) $[M - C_4H_8]^+$, 347 (15) $[M - C_7H_7]^+$, 337 (7) $[M - C_4H_9, CO_2]^+$, 291 (10), 247 (75) $[C_{13}H_{15}N_2O_3]^+$, 186 (24), 91 (100)

$[C_7H_7]^+$. HRMS: calcd. for $C_{25}H_{30}N_2O_5$ $[M]^+$ 438.2155; found 438.2157.

Crystal Structure Determination of *rac*-(4*S*)-25: The single-crystal X-ray diffraction study of *rac*-(4*S*)-**28** was carried out with a Bruker–Nonius Kappa-CCD diffractometer at 123(2) K using Mo-K_α radiation (λ = 0.71073 Å). Direct methods (SHELXS-97) were used for structure solution, and refinement was carried out using SHELXL-97[26] (full-matrix least-squares on F^2). Non-hydrogen atoms were refined anisotropically, hydrogen atoms were localized by difference electron-density determination and refined using a riding model [H(O) free]. The solvent pentane is disordered about a center of symmetry. *rac*-(4*S*)-**25**: colorless crystals, $C_{29}H_{30}N_2O_6 \cdot 0.5C_5H_{12}$, M = 538.62, crystal size: 0.15 × 0.10 × 0.05 mm, triclinic, space group $P\bar{1}$ (No. 2), a = 10.528(1) Å, b = 11.781(2) Å, c = 13.104(2) Å, α = 116.05(2)°, β = 95.20(2)°, γ = 104.29(2)°, V = 1377.5(3) Å^3, Z = 2, ρ(calc) = 1.299 Mg m^{-3}, F(000) = 574, μ = 0.090 mm^{-1}, 16581 reflections ($2\theta_{max}$ = 50°), 4815 unique [R_{int} = 0.063], 357 parameters, 14 restraints, $R1$ [$I > 2\sigma(I)$] = 0.058, $wR2$ (all data) = 0.141, S = 1.01, largest diff. peak and hole: 0.844 and –0.349 e Å^{-3}.

CCDC-823873 [for *rac*-(4*S*)-**25**] contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Supporting Information (see footnote on the first page of this article): Experimental data for **11**, *rac*-**12**, and ethyl *rac*-(*E*)-5-(*tert*-butoxycarbonylamino)-5-(furan-2-yl)pent-2-enoate and spectroscopic data for all new compounds.

Acknowledgments

We thank the Deutsche Forschungsgemeinschaft (DFG) (BR 1750/17-1 and SCHN 441/7–1) and the Fonds der Chemischen Industrie (fellowship to B. M. R.) for financial support. We gratefully acknowledge the valuable experimental assistance of Simone Grässle.

[1] a) P. Wipf, Y. Kim, D. M. Goldstein, *J. Am. Chem. Soc.* **1995**, *117*, 11106–11112; b) P. Wipf, S. R. Spencer, *J. Am. Chem. Soc.* **2005**, *127*, 225–235.
[2] a) J. P. Bäckvall, G. J. Andersson, *J. Am. Chem. Soc.* **1990**, *112*, 3683–3685; b) M. P. Yeh, W. Yeh, L. Tu, J. Wu, *Tetrahedron* **2009**, *65*, 4789–4794.
[3] T. Meng, Y. Hu, Y. Sun, T. Zhu, S. Wang, *Tetrahedron* **2010**, *66*, 8648–8653.
[4] W. Oppolzer, W. Fröstl, *Helv. Chim. Acta* **1975**, *58*, 590–593.
[5] R. X. Tan, P. R. Jensen, P. G. Williams, W. Fenical, *J. Nat. Prod.* **2004**, *67*, 1374–1382.
[6] J.-M. Wang, G.-Z. Ding, L. Fang, J.-G. Dai, S.-S. Yu, Y.-H. Wang, X.-G. Chen, S.-G. Ma, J. Qu, S. Xu, D. Du, *J. Nat. Prod.* **2010**, *73*, 1240–1249.
[7] T. Fukuyama, S.-I. Nakatsuka, Y. Kishi, *Tetrahedron* **1981**, *37*, 2045–2078.
[8] K. C. Nicolaou, S. Totokotsopoulos, D. Giguère, Y.-P. Sun, D. Sarlah, *J. Am. Chem. Soc.* **2011**, *133*, 8150–8153.
[9] J. E. DeLorbe, S. Y. Jabri, S. M. Mennen, L. E. Overman, F.-L. Zhang, *J. Am. Chem. Soc.* **2011**, *133*, 6549–6552.
[10] a) (+)-11,11′-Dideoxyverticillin A: J. Kim, J. A. Asenhurst, M. Movassaghi, *Science* **2009**, *324*, 238–241; b) (+)-Chaetoxin A: E. Iwasa, Y. Hamashima, S. Fujishiro, E. Higuchi, A. Ito, M. Yoshida, M. Sodeoka, *J. Am. Chem. Soc.* **2010**, *132*, 4078–4079; c) (+)-Chaetocin A and C and (+)-12,12′-Dideoxychetracin A: J. Kim, M. Movassaghi, *J. Am. Chem. Soc.* **2010**, *132*, 14376–14378.
[11] a) U. Gross, M. Nieger, S. Bräse, *Org. Lett.* **2009**, *11*, 4740–4742; b) U. Gross, M. Nieger, S. Bräse, *Chem. Eur. J.* **2010**, *16*, 11624–11631.
[12] A. Harvey, *Drug Discov. Today* **2000**, *5*, 294–300.
[13] a) M. Sickert, C. Schneider, *Angew. Chem. Int. Ed.* **2008**, *47*, 3631–3634; b) M. Sickert, F. Abels, M. Lang, J. Sieler, C. Birkemeyer, C. Schneider, *Chem. Eur. J.* **2010**, *16*, 2806–2818. c) After optimization, the vinylogous Mukaiyama–Mannich reaction proceeded in 89% *ee*. For first studies, we used 81% *ee* enriched material and determined the optical purity for compounds **16** and **18** to prove the persistency of the *ee* values.
[14] S. E. Denmark, G. L. Beutner, *J. Am. Chem. Soc.* **2003**, *125*, 7800–7801.
[15] J. M. M. Verkade, L. J. C. van Hemert, P. J. L. M. Quaedflieg, P. L. Alsters, F. L. van Delft, F. P. J. T. Rutjes, *Tetrahedron Lett.* **2006**, *47*, 8109–8113.
[16] Details of the structure, synthesis, and spectroscopy of the Boc-protected product can be found in the Supporting Information.
[17] Conditions of this transformation have been previously optimized, see: A. Friedrich, M. Jainta, C. F. Nising, S. Bräse, *Synlett* **2008**, 589–591.
[18] *exo* refers to the orientation of the ethyl ester substituent of the dienophile towards the diene.
[19] K. B. Sharpless, W. Amberg, Y. L. Benanni, G. A. Crispino, J. Hartung, K. S. Jeong, H. L. Kwong, K. Morikawa, Z. M. Wang, *J. Org. Chem.* **1992**, *57*, 2768–2771.
[20] R. B. Woodward, F. V. Brutcher Jr, *J. Am. Chem. Soc.* **1958**, *80*, 209–211.
[21] P. Li, J. N. Payette, H. Yamamoto, *J. Am. Chem. Soc.* **2007**, *129*, 9534–9535.
[22] For the initial studies we used the racemic product of the vinylogous Mannich reaction (the synthesis of which can be found in the Supporting Information) throughout the whole synthetic sequence before accomplishing the most important steps with enantiomerically enriched material.
[23] T. Shioiri, K. Ninomiya, S. Yamada, *J. Am. Chem. Soc.* **1972**, *94*, 6203–6205.
[24] a) A. Friedrich, M. Jainta, M. Nieger, S. Bräse, *Synlett* **2007**, 2127–2129; b) M. Jainta, M. Nieger, S. Bräse, *Eur. J. Org. Chem.* **2008**, 5418–5424.
[25] Due to the occurrence of rotamers in all Cbz-substituted hydroindoles, most of the signals in the ^{1}H NMR spectra appear to be broad singlets or multiplets without assignable multiplicity, whereas most of the signals in the ^{13}C NMR are duplicated. High-temperature measurements in deuterated toluene sharpened signals, but could not bring full clarity as the ceiling temperature exceeded 373 K.
[26] G. M. Sheldrick, *Acta Crystallogr., Sect. A* **2008**, *64*, 112–122.
Received: July 8, 2011
Published Online: September 14, 2011

