Enantioselective Construction of Highly Functionalized Indoloquinolizines—Congeners to Polycyclic Indole Alkaloids

Ralf Lock and Herbert Waldmann*

Abstract: Indolo[2,3-*a*]quinolizines have been prepared in enantiomerically pure form by a very short and efficient synthetic sequence consisting of a) formation of imines of tryptophan esters, b) their enantioselective reaction with substituted silyloxydienes mediated by a chiral or an achiral boron Lewis acid, and c) subsequent ring closure initiated by conversion of the generated vinylogous amides into vinylogous imidoyl chlorides. With this strategy various substituents can be incorporated directly into the 1-position of the heterocyclic framework of complex indole alkaloids by the choice of an appropriate silyloxydiene, so that subsequent derivatization of the alkaloid precursor at this position is rendered unnecessary.

Keywords
alkaloids · asymmetric catalysis · asymmetric synthesis · indoles · Mannich reactions

Introduction

Numerous polycyclic indole alkaloids, for example, of the eburnamine and vincamine type, and of the reserpine, yohimbine, and corynantheidine type mediate a variety of physiological effects and are advantageously employed for pharmaceutical purposes. The stereoselective synthesis of these natural products and analogues thereof with modified biological properties is, therefore, of great interest in organic synthesis in general and in natural product, heterocyclic, and medicinal chemistry in particular.[1–3]

The underlying heterocyclic framework that is common to these alkaloids is the indolo[2,3-*a*]quinolizidine structure **2**, which, in the case of eburnamine (**1**), is further functionalized at C-1 (Scheme 1). A viable strategy for their synthesis would, therefore, consist of a short and efficient construction of appropriately substituted enantiomerically pure indolo[2,3-*a*]-quinolizidines and their subsequent elaboration to the desired target compounds.[1–4] We have previously shown that this goal can, in principle, be reached by the construction of enaminones **3**, which are obtained from Schiff bases **4** derived from tryptophan and electron-rich silyloxydienes such as **5** in one step, and their cyclization to give indolo[2,3-*a*]quinolizidones, for instance, the ketone (+)-**6**.[5, 6] To gain access to, for example, the eburnamine-type alkaloids from **6**, a further substituent must be introduced at C-1. As a result, the overall synthesis is considerably lengthened and the question raised of how to introduce a substituent into the sterically less accessible 1-position of the tetracyclic ketone stereo- and regioselectively.

These problems could be solved elegantly if the required substituent R^1 would be incorporated from the beginning into the enaminone **3** so that the appropriately substituted precursor **2** would be formed on cyclization of **3**. Since C-1 of the indolo-[2,3-*a*]quinolizidines **2** is derived from C-2 of the electron-rich dienes **5**, this strategy might be realized by the use of silyloxydienes of the type **5** bearing the required additional substituents.[7]

We note that by means of the same strategy indole alkaloids with substituents in the 3-position of the basic indolo[2,3-*a*]-quinolizidine system (see **2**; for example, alkaloids of the reserpine type, the yohimbine type, the corynantheidine type, and oxindole alkaloids) should be accessible from dienes of type **5** bearing an appropriate substituent at C-4.

The purpose of this paper is to report in full detail on the successful implementation of this concept by the highly stereoselective two-step synthesis of 1-substituted indoloquinolizines via the intermediate generation of enaminones of type **3** from imines **4** derived from tryptophan ester and a siloxydiene **5** carrying a substituent at C-2 (R^1 = Et), followed by ring closure to the tetracyclic indole bases **2**.[8]

Results and Discussion

The ethyl-substituted silyloxydiene **13** was chosen as a candidate to investigate whether the above-mentioned synthetic strategy could be successfully realized. Compound **13** was synthesized from 2-pentanone by first converting this ketone into the trimethylsilylenol ether **8** according to House et al.[9] and subse-

[*] Prof. Dr. H. Waldmann, Dr. R. Lock
Institut für Organische Chemie der Universität Karlsruhe
Richard-Willstätter-Allee 2, D-76128 Karlsruhe (Germany)
Fax: Int. code +(721)608-4825
e-mail: waldmann@ochhades.chemie.uni-karlsruhe.de

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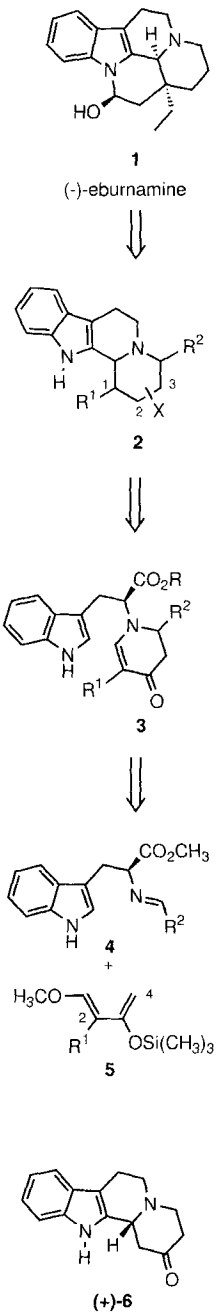
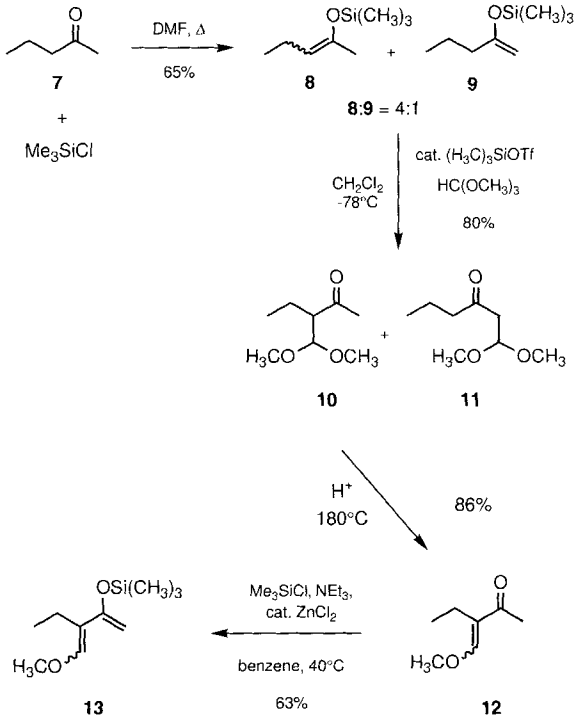


Scheme 1. Retrosynthetic analysis of highly functionalized tetracyclic indole alkaloids.

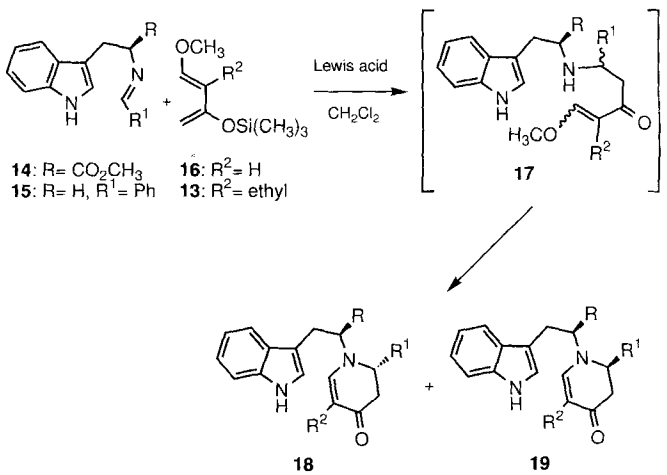
quent reaction with trimethylorthoformate to give the acetal **10** according to Noyori et al.[10] (Scheme 2). In the course of this two-step sequence the ether **9** and the respective acetal **11** were also formed. Whereas **8** and **9** could not be separated, **10** was readily obtained pure by distillation. After acid-catalyzed elimination of methanol from **10** to produce the enol ether **12**, the desired electron-rich diene **13** was obtained in useful yield by enolization and O-silylation of the ketone.

The silyloxydiene **13** was then subjected to the Lewis acid mediated reaction with imine **14**[5] derived from tryptophan methyl ester (Scheme 3).

The ensuing reaction proceeds by attack of the silylenol ether moiety of **13** on the Schiff base to generate the intermediate vinylogous esters **17**, which subsequently undergo cyclization to the enaminones **18** and **19**. In initial experiments catalysis of this tandem Mannich–Michael process by $ZnCl_2$ was investigated. Although this Lewis acid had proven to be the catalyst of choice in reactions employing the unsubstituted diene **16**,[5] it failed to promote the reaction between the diene **13** and the imine **14** with preparatively useful results, in particular with undesirably low stereoselectivity. The situation was significantly improved by using triphenyl borate at $-78\,^{\circ}C$, as recommended by Yamamoto et al. for related transformations.[11] In the presence of this Lewis acid the enaminones **18** and **19** were smoothly formed in yields of up to 61% (for two steps; i.e., from tryptophan methyl ester hydrochloride) and with diastereomer ratios of up to 98:2 (Scheme 3; Table 1, entries 4 and 7–10). The tandem process can be carried out with imines derived from aromatic or aliphatic aldehydes (Table 1, entries 4–10). The absolute configuration of the newly formed stereocenters was determined by conversion of **18** to indoloquinolizines and subsequent analysis of their configuration by means of NMR spectroscopic techniques (vide infra). Variation of the amount of the Lewis acid from 0.1 to 2 equivalents did not result in any change in the stereoselectivity. However, the highest yields were obtained in the presence of one equivalent of the boron catalyst. The use of a boric acid phenyl ester as the reagent of choice opened up the possibility of further enhancing the level of stereoselectivity by applying the principle of double diastereoselection,[12] that is, by using a



Scheme 2. Syntheses of the ethyl-substituted siloxy diene **13**.



Scheme 3. Tandem Mannich–Michael reactions employing Schiff bases of tryptophan methyl ester.

chiral catalyst. To this end, enantiomerically pure boric acid binaphthyl esters **20** and **21** were prepared from boric acid triphenyl ester and (*R*)- or (*S*)-binaphthol, as described by Yamamoto et al.[11] A significant enhancement of the diastereomer ratio from 93:7 to 96:4 was observed for the reaction of the electron-rich diene **13** with the imine derived from benzaldehyde and (*S*)-tryptophan methyl ester (**14**, R = CO_2CH_3, R^1 = Ph) mediated by boric acid ester **20**. In contrast, only a slight enhancement (to 94:6) was recorded for the catalyst **21** derived

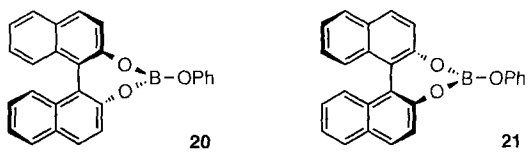


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Table 1. Results of the Mannich–Michael reactions employing the imines **14** and **15** and the dienes **13** and **16**.

Entry	**18,19**	R	R^1	R^2	T/°C	Lewis Acid	Yield/% [a]	**18**:**19** [a,b]
1	**a**	CO_2CH_3	phenyl	H	−78	$B(OPh)_3$	51	88:12
2	**a**	CO_2CH_3	phenyl	H	−40	**20**	34	95:5
3	**a**	CO_2CH_3	phenyl	H	−40	**21**	24	91:9
4	**b**	CO_2CH_3	phenyl	ethyl	−78	$B(OPh)_3$	61	93:7
5	**b**	CO_2CH_3	phenyl	ethyl	−40	**20** [c]	53	96:4
6	**b**	CO_2CH_3	phenyl	ethyl	−40	**21**	40	94:6
7	**c**	CO_2CH_3	4-Cl-C_6H_4	ethyl	−78	$B(OPh)_3$	38	91:9
8	**d**	CO_2CH_3	4-NO_2-C_6H_4	ethyl	−78	$B(OPh)_3$	35	94:6
9	**e**	CO_2CH_3	heptyl	ethyl	−78	$B(OPh)_3$	31	90:10
10	**f**	CO_2CH_3	2-propyl	ethyl	−78	$B(OPh)_3$	29	>98:2
11	**g**	H	phenyl	ethyl	−60	**20** [c]	62	63:37 [d]

[a] All yields refer to tryptophan methyl ester hydrochloride. [b] Determined by integration of the signals found in the NMR spectra for 6-H and α-H of the diastereomers **18**, **19**. [c] 0.5 equiv Lewis acid. [d] Determined by HPLC with a chiral column, see Experimental Section.

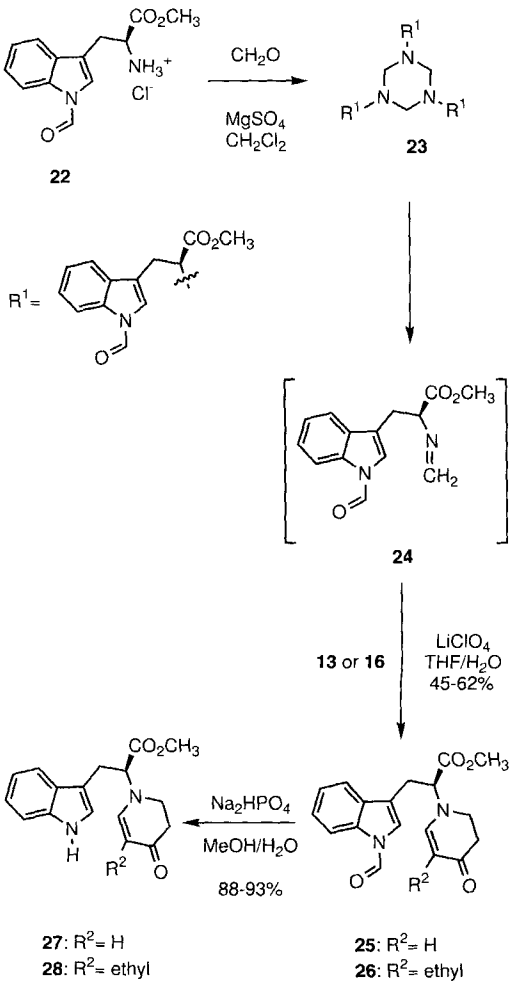
from (*S*)-binaphthol (Table 1, entries 4–6). In the presence of the binaphthol Lewis acids **20** and **21** the reaction was slower, so the reaction temperature was raised to −40 °C. In these transformations, variation of the amount of the Lewis acid from 0.1 to 1.5 equivalents also failed to influence the stereoselectivity. The highest yield, however, was obtained in the presence of 0.5 equivalents of **20**.

The results recorded for the tandem Mannich–Michael reaction of the imine **14** with the unsubstituted silyloxydiene **16** were also significantly improved when boric acid esters were employed as Lewis acid catalysts. Thus, in the presence of $ZnCl_2$ **18a** and **18b** (R^1 = Ph) were obtained in a ratio of 70:30;[5] when boric acid triphenyl ester was used this ratio was increased to 88:12 (Table 1, entry 1). When the chiral binaphthol catalyst **20** was employed, the diastereomer ratio was further raised to 95:5, whereas **21** yielded an isomer ratio of 91:9. To determine the degree of stereoselectivity conferred by the chiral boron Lewis acids and their intrinsic stereopreference, the reaction of diene **13** with the achiral imine **15** was investigated. Only a low enantioselectivity was obtained for the conversion of compound **15** (R^1 = Ph) to the enaminones **18g** and **19g** in the presence of boric acid ester **20** (Table 1, entry 11). The predominant isomer was shown to be **18g** by generating it from **18b** (R = CO_2CH_3, R^1 = Ph). Thus, the methyl ester in **18b** was saponified and the resulting carboxylic acid decarboxylated according to the Barton procedure[13] to give **18g** of known absolute configuration. Comparison of the specific rotations and the retention times in HPLC using a column with a chiral stationary phase proved **18g** to be the (6*R*) isomer (see the Experimental Section).

In the transformations detailed above the principle of double diastereoselectivity is clearly operative, with the (*S*)-tryptophan-derived Schiff bases and the (*R*)-binaphthol-substituted boron Lewis acid forming the "matched" pair.

In the Lewis acid mediated reactions of the imines **14** and **15** with the dienes **13** and **16** a competing direct Pictet–Spengler type cyclization of **14** and **15** to the respective tetrahydro-β-carbolines was not observed.

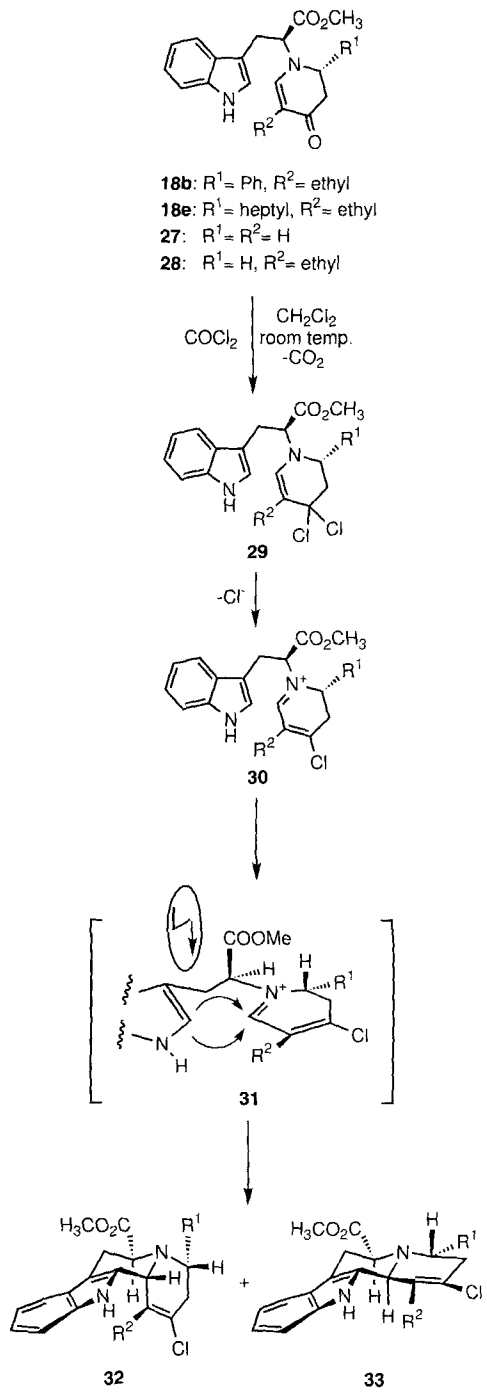
The substituent "R^1" in the enaminones **18** and **19** can be used to construct various 4-substituted indoloquinolizines (vide infra), which may be converted into analogues of natural products and physiologically relevant heterocycles. For the construction of polycyclic indole alkaloids themselves, however, a methylene group is required at this position since the naturally occurring nitrogen bases do not carry an alkyl or aryl residue at the respective carbon atom. Consequently, the formaldehyde imine of tryptophan methyl ester must be employed to prepare these compounds, and it is recommended to protect the indole nitrogen with an electron-withdrawing group to prevent undesired side reactions of the aromatic ring with formaldehyde in the course of the imine formation. In the past we have used the benzyloxycarbonyl group for this purpose,[5] introduced in a three-step sequence, but the formyl group turned out to be more advantageous. N^{ind}-Formyl masked tryptophan methyl ester **22**



Scheme 4. Tandem Mannich–Michael reactions employing the formaldimine **24** of tryptophan methyl ester.

was readily prepared in one step[14] and converted on treatment with formaldehyde into the aldimine, which is present as trimer or oligomer (Scheme 4). In the presence of a Lewis acid **23** was transformed in situ into the monomer **24**, which reacted with added diene **13** or **16** to give the desired enaminones **25** and **26**. Finally, the formamides could be saponified selectively under mildly basic conditions to liberate the vinylogous amides **27** and **28** in high yield (Scheme 4). When the reaction between the imine **24** and the dienes **13** or **16** was promoted with $ZnCl_2$ only low yields of the enaminones **25** and **26** were obtained. The use of 10 equivalents of $LiClO_4$ in aqueous THF, however, gave significantly better results. The presence of 5–20 vol% of water in the solvent is necessary; in anhydrous THF the reaction does not take place. Attempts to catalyze the reaction in the aqueous medium with lanthanide triflates as described by Kobayashi et al.[15] were less successful.

To build up the basic tetracyclic indoloquinolizine ring system of polycyclic indole alkaloids and analogues thereof from the enaminones synthesized as described above, the ring closure through attack of the electron-rich indole nucleus on the double bond of the vinylogous amide had to be induced. Whereas in the case of the enaminones generated from the unsubstituted diene **16** this could be realized by simple treatment with an acid (e.g., CF_3COOH or HBr/AcOH), in the case of the respective ethyl-substituted analogues obtained from **13**, the use of simple Brønstedt acids was unsuccessful. Attempts to induce the conversion of these vinylogous amides into iminium intermediates by O-alkylation with oxonium salts or by O-silylation also remained fruitless. We resorted, therefore, to the application of a synthetic method that has previously been used in an entirely different context,[16] but not in the construction of polycyclic alkaloids:[17] an amide is converted into a chloromethylamine that then eliminates a chloride ion to give an imidoyl chloride. Thus, on treatment of the vinylogous amides **18b**, **18e**, **27** and **28** with phosgene, the corresponding vinylogous chloromethylamines **29** were formed, which were converted in situ into the vinylogous imidoyl chlorides **30** (Scheme 5). These electrophiles then underwent a rapid intramolecular attack of the indole nucleus on the generated iminium function to give rise to the cyclization products **32** and **33** (Scheme 5, Table 2). When R^1 is H or phenyl the indole preferably approaches the *Si* side of the $C{=}N^+$ double bond, that is, *anti* to the $COOCH_3$ group, which is more favorable for steric reasons (see **31**, Scheme 5), and the isomers **32** are formed in excess. When R^1 is heptyl the diastereomer **33** is favored through attack from the *Re* side, that is, *syn* to the $COOCH_3$ group. We currently have no conclusive rationale for this difference in the steric course of the reaction. It should be noted, however, that the reaction most probably



Scheme 5. Cyclization of the didehydropiperidine-4-ones **18** to indolo[2,3-*a*]-quinolizines.

Table 2. Cyclization of the didehydropiperidine-4-ones to indolo[2,3-*a*]quinolizines.

Entry	32,33	R^1	R^2	Yield/%	*cis*:*trans* [a]		δ(12b-H)	
					32	33	32	33
1	a	H	H	46	3.6	1	5.00	4.85
2	b	H	ethyl	54	2	1	5.07	4.88
3	c	Ph	ethyl	59	1.5	1	5.19	5.09
4	d	heptyl	ethyl	49	1	2.5	5.11	4.93

[a] Determined from the 250 and 400 MHz ^{1}H NMR spectra.

proceeds through attack of C-3 of the indole nucleus on the electrophile leading to the formation of a *spiro* intermediate,[18] which then undergoes a Wagner–Meerwein type rearrangement. It is, therefore, possible that both steric and electronic arguments must be considered to explain the outcome of the cyclization reactions depicted in Scheme 5.

The conformation of the indoloquinolizines **32** and **33** was analyzed by NMR spectroscopy. The two six-membered rings in **32** are found to be in a *cis* orientation, whereas **33** adopts a *trans* decalin conformation. This conclusion was reached based on two pieces of evidence, namely, NOEs and chemical shifts. NOE

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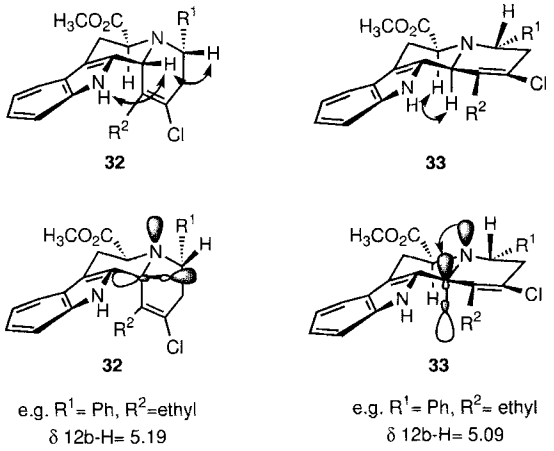
signals are observed between the indole N-H and 12b-H and between 12b-H and 4-H in **32**, and between 12b-H and 6-H in **33** (Scheme 6). In the *trans* decalin-type isomers **33** the lone pair on the nitrogen is oriented parallel to the σ* orbital of the C-12b–12b-H bond, whereas in the *cis* decalin isomers **32** these orbitals are oriented perpendicular to each other (Scheme 6).



Scheme 6. Analysis of the structure of the indolo[2,3-*a*]quinolizines **32** and **33** by NMR techniques.

Therefore, in **33** the electron density in the C-12b–H-12b bond is increased by electron donation into the σ* orbital, but for stereoelectronic reasons not in the case of **32**. Consequently, the 12b-H atoms of the *trans* isomers **33** are more shielded and appear at a higher field, that is, with lower chemical shift values in the NMR spectra (Table 2).[19]

Conclusion

We have devised an efficient synthetic route to indolo[2,3-*a*]-quinolizines that makes these chiral tetracyclic indole bases available from tryptophan methyl ester with very high stereoselectivity in only three steps (imine formation–reaction with a diene–cyclization). By means of this strategy various substituents can be incorporated directly into the 1-position of the heterocyclic framework by the choice of an appropriate silyloxydiene. Subsequent regioselective derivatization of the alkaloid precursor is therefore no longer necessary. Finally, the vinyl chloride functionality generated in the terminal six-membered ring opens up many possibilities for the rapid and selective introduction of further substituents and the attachment of rings, for example, through Heck-type processes or after hydrolysis to the ketone.

Experimental Section

General: All melting points were recorded on a Büchi melting point apparatus and are uncorrected. Infrared spectra were taken with a Bruker IFS88 spectrometer. Proton and carbon NMR spectra were measured on a Bruker AC-250, a Bruker AM-400 or a Bruker DRX-500 spectrometer. Chemical shifts are expressed in ppm downfield relative to tetramethylsilane as an internal standard. Specific optical rotation values were determined on a Perkin Elmer polarimeter 241. Mass spectra were taken with a Finnigan MAT 90 spectrometer. Elemental analyses were performed on an Elementar CHN-Rapid analyzer. HPLC was performed on a Merck Hitachi instrument equipped with an L-3000 diode array detector, using a ZWE 376 A column, kindly supplied by Bayer, and THF/hexane 60:40 (*v*:*v*) as eluent, flow 1 mL min^{-1}. Medium-pressure liquid chromatography (MPLC) was performed on a Büchi 681 or Büchi 684, using Merck silica gel 60 (15–40 μm). For thin-layer chromatograpy (TLC) Merck silica gel 60 F254 layers were used. Flash chromatography was performed with Baker silica gel (40–60 μm). Distillation was performed with a Fischer Spaltrohrdestille HMS 500.

Materials: Tryptophan was kindly donated by Degussa. The Schiff bases were prepared by condensation of tryptophan methyl ester with the respective aldehyde in the presence of magnesium sulfate in dichloromethane [5]. Filtration, followed by evaporation of the solvent in vacuo, afforded the imines as yellowish oils.

3,3-Dimethoxymethylpentan-2-one (10) and 1,1-dimethoxyhexan-3-one (11): 2-Pentanone was transformed into its silyl enol ether as described by House et al. [9] yielding an inseparable mixture of **8** and **9** in a ratio of 4:1. To a solution of this mixture (42.79 g, 0.27 mol) and trimethyl orthoformate (28.68 g, 0.27 mol) in dichloromethane (300 mL), molecular sieves 4 Å (10 g) were added, and the mixture was cooled to −78 °C. After addition of trimethylsilyl trifluoromethanesulfonate (0.3 mL, 0.369 g, 1.7 mmol) the solution was stirred at this temperature for 6 h, followed by the additon of a saturated solution of $NaHCO_3$ in water (50 mL) and warming up to room temperature. The layers were separated, and the aqueous phase was extracted twice with dichloromethane (50 mL). The combined organic phases were dried with $MgSO_4$, and the solvent was removed in vacuo. The residue was fractionated by distillation using a Fischer Spaltrohr column and yielded 26.23 g (61%) of **10** and 4.6 g (11%) of **11**.

10: colorless liquid, b.p. 61–62 °C (12–15 mbar). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 4.40$ (d, $J_{6-H,3-H} = 8$ Hz, 1H, 6-H), 3.33 (s, 6H, OCH_3), 2.80 (ddd, $J_{3-H,6-H} = 8$ Hz, $J_{3-H,4-Ha} = 8$ Hz, $J_{3-H,4-Hb} = 5$ Hz, 1H, 3-H), 2.18 (s, 3H, 1-H), 1.74–1.52 (m, 2H, 4-H), 0.88 (t, $J_{vic} = 7$ Hz, 3H, 5-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 210$ (C-2), 105.4 (C-6), 57.0 (C-3), 55.2 (OCH_3), 52.6 (OCH_3), 31.6 (C-1), 21.3 (C-4), 11.6 (C-5). MS (70 eV): *m*/*z* (%) = 160 [M^+] (0.2). $C_8H_{16}O_3$ calcd 160.1099, found 160.1087 (MS).

11: colorless liquid, b.p. 71–72 °C (12–15 mbar). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 4.80$ (t, $J_{vic} = 6.5$ Hz, 1H, 1-H), 3.35 (s, 6H, OCH_3), 2.71 (d, $J_{vic} = 6.5$ Hz, 2H, 2-H), 2.42 (t, $J_{vic} = 7$ Hz, 2H, 4-H), 1.68–1.52 (m, 2H, 5-H), 0.91 (t, $J_{vic} = 7$ Hz, 3H, 6-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 207.6$ (C-3), 101.7 (C-1), 53.8 (OCH_3), 46.4 (C-2), 45.8 (C-4), 16.8 (C-5), 13.6 (C-6). MS (70 eV): *m*/*z* (%) = 160 [M^+] (11). $C_8H_{16}O_3$ calcd 160.1099, found 160.1086 (MS).

3-Methoxymethylenepentan-2-one (12): To **10** (26.23 g, 0.164 mol) *p*-toluene sulfonic acid (0.2 g) was added and the mixture was heated to 180 °C for 5 h. After cooling to room temperature the mixture was distilled under reduced pressure, yielding 13.24 g (63%) of the α,β-unsaturated ketone **12**; colorless liquid, b.p. 70–73 °C (13 mbar). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 7.17$ (s, 1H, 6-H), 3.86 (s, 3H, OCH3), 2.25 (q, $J_{vic} = 7$ Hz, 2H, 4-H), 2.20 (s, 3H, 1-H), 0.92 (t, $J_{vic} = 7$ Hz, 3H, 5-H). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 196.8$ (C-2), 160.2 (C-6), 124.1 (C-3), 61.4 (OCH_3), 25.3 (C-1), 16.2 (C-4), 13.2 (C-5). MS (70 eV): *m*/*z* (%) = 128 [M^+] (57). $C_7H_{12}O_2$ calcd 128.0837, found 128.0823 (MS).

Diene 13: To a suspension of $ZnCl_2$ (0.2 g) in benzene (30 mL) triethylamine (27 g, 0.267 mol), **12** (13.24 g, 0.1 mol) and chlorotrimethylsilane (21.73 g, 0.2 mol) were added. The mixture was stirred under nitrogen at 40 °C for 18 h. After the reaction mixture had cooled to room temperature, 200 mL of diethyl ether was added, the solid was removed by filtration, and the solvent evaporated in vacuo. Distillation delivered 13.2 g of a mixture that contained 80% siloxy diene and 20% starting material. This mixture was used for the following transformations without further purification. Colorless liquid, b.p. 72–73 °C (15 mbar). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 6.30$ (s, 1H, 6-H), 4.12 (s, 1H, 1-Ha), 4.00 (s, 1H, 1-Hb), 3.50 (s, 3H, OCH_3), 2.04 (q, $J_{vic} = 7$ Hz, 2H, 4-H), 0.85 (t, $J_{vic} = 7$ Hz, 3H, 5-H), 0.05 (s, 9H, $Si(CH_3)_3$). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 154.7$ (C-2), 146.6 (C-6), 118.1 (C-3), 89.1 (C-1), 60.0 (OCH_3), 18.0 (C-4), 13.4 (C-5), 0.1 ($Si(CH_3)_3$). MS (70 eV): *m*/*z* (%) = 200 [M^+] (41), 185 (72), 171 (58), 170 (20), 169 (56), 113 (34), 89 (20), 75 (27), 73 (100), 45 (9), 43 (8). $C_{10}H_{20}O_2Si$ calcd 200.1233, found 200.1218 (MS).

2,3-Didehydropiperidin-4-ones 18 and 19: To a solution of of the imine (3 mmol) in dichloromethane (30 mL), powdered 4 Å molecular sieves (0.5 g) was added. The mixture was cooled to 0 °C, and a 1 M solution of boric acid triphenyl ester in dichloromethane (3 mL, 3 mmol) was added. The mixture was stirred for 10 min and cooled to −78 °C. A solution of the diene **16** (0.9 g, 5 mmol, 1.7 eq) or of the diene **13** (1 g, 4 mmol, 1.4 equiv), in dichloromethane (5 mL) was added dropwise. The mixture was allowed to warm up in 7–10 h and was stirred overnight at room temperature. After filtration the solution was extracted with 1 M hydrochloric acid (20 mL) and Na_2CO_3 solution (20 mL). The organic phase was dried with $MgSO_4$, the solvent removed in vacuo, and the products were isolated from the remaining residue by flash chromatography on silica gel using hexane/acetone mixtures as eluents.

18a and 19a: These compounds have been described in ref. [5].

18b and 19b: colorless amorphous solid, yield 61%, R_f = 0.26 (hexane/acetone 2:1 (*v*:*v*)). $C_{25}H_{26}N_2O_3$ calcd C 74.60, H 6.51, N 6.96; found C 74.41, H 6.59, N 6.98. The diastereomers were separated by MPLC on silica gel using dichloromethane/ethanol 1000:5 (*v*:*v*) as eluent.

(6*S*)-*N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-3-ethyl-4-oxo-6-phenyl-2,3-didehydropiperidine (18b): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.75 (brs, 1H, N-H), 7.40–6.82 (m, 11H, 5Ph-H, In 2-H, In 4-H, In 5-H, In 6-H, In 7-H, 2-H), 4.57 (dd, $J_{6-H,5-Ha}$ = 13 Hz, $J_{6-H,5-Hb}$ = 6 Hz, 1H, 6-H), 3.88 (dd, J_{vic} = 9 Hz, $J_{vic'}$ = 7 Hz, 1H, CH_2CHCO_2), 3.61 (s, 3H, OCH_3), 3.40 (dd, J_{gem} = 15 Hz, $J_{vic'}$ = 7 Hz, 1H, $CH_{2a}CHCO_2$), 3.12 (dd, J_{gem} = 15 Hz, J_{vic} = 9 Hz, 1H, $CH_{2b}CHCO_2$), 2.65 (dd, J_{gem} = 16 Hz, $J_{5-Ha,6-H}$ = 13 Hz, 1H, 5-Ha), 2.55 (dd, J_{gem} = 16 Hz, $J_{5-Hb,6-H}$ = 6 Hz, 1H, 5-Hb), 2.25 (q, J_{vic} = 8 Hz, 2H, CH_2CH_3), 1.05 (t, J_{vic} = 8 Hz, CH_2CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 190.8 (C-4), 171.4 (CO_2Me), 148.5 (C-2), 138.1 (Ph C-*ipso*), 136.1 (In C-7a), 128.7 (2 Ph C), 128.3 (Ph C-*para*), 127.3 (2 Ph C), 127.0 (In C-3a), 123.3 (In C-2), 121.9 (In C-6), 119.3 (In C-5), 118.1 (In C-4), 114.4 (C-3), 111.3 (In C-7), 109.7 (In C-3), 64.1 (CH_2CHCO_2), 61.4 (C-6), 52.1 (OCH_3), 44.8 (C-5), 26.8 (CH_2CHCO_2), 20.5 (CH_2CH_3), 14.4 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1739 (C=O, ester), 1596 (C=O, vinylogous amide) cm^{-1}. MS (70 eV): *m*/*z* (%) = 403 [M^+ + H] (8), 402 [M^+] (31), 273 (39), 272 (16), 168 (14), 131 (9), 130 (100). $C_{25}H_{26}N_2O_3$ calcd 402.1943, found 402.1914 (MS). $[\alpha]_D^{20}$ = −65.2 (*c* = 1.05, CH_2Cl_2).

(6*R*)-*N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-3-ethyl-4-oxo-6-phenyl-2,3-didehydropiperidine (19b): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.80 (brs, 1H, N-H), 7.40–7.12 (m, 7H, 5 Ph-H, 2 In-H), 7.05 (t, $J_{In5-H,In4-H}$ = $J_{In5-H,In6-H}$ = 8 Hz, 1H, In 5-H), 6.97–6.86 (m, 3H, 2 In-H, 2-H), 4.06 (dd, J_{vic} = 10 Hz, $J_{vic'}$ = 6 Hz, 1H, CH_2CHCO_2), 3.97 (dd, $J_{6-H,5-Ha}$ = 10 Hz, $J_{6-H,5-Hb}$ = 7 Hz, 1H, 6-H), 3.65 (s, 3H, OCH_3), 3.35 (dd, J_{gem} = 15 Hz, $J_{vic'}$ = 6 Hz, 1H, $CH_{2a}CHCO_2$), 3.16 (dd, J_{gem} = 15 Hz, J_{vic} = 10 Hz, 1H, $CH_{2b}CHCO_2$), 2.55 (dd, J_{gem} = 16 Hz, $J_{5-Ha,6-H}$ = 10 Hz, 1H, 5-Ha), 2.44 (dd, J_{gem} = 16 Hz, $J_{5-Hb,6-H}$ = 7 Hz, 1H, 5-Hb), 2.24 (q, J_{vic} = 8 Hz, 2H, CH_2CH_3), 1.09 (t, J_{vic} = 8 Hz, CH_2CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 190.0 (C-4), 171.5 (CO_2Me), 148.8 (C-2), 138.9 (Ph C-*ipso*), 136.3 (In C-7a), 128.7 (2 Ph C), 128.1 (Ph C-*para*), 127.1 (2 Ph C), 126.6 (In C-3a), 123.6 (In C-2), 122.2 (In C-6), 119.5 (In C-5), 118.2 (In C-4), 113.4 (C-3), 111.5 (In C-7), 109.7 (In C-3), 64.5 (CH_2CHCO_2), 62.8 (C-6), 52.3 (OCH_3), 44.4 (C-5), 28.3 (CH_2CHCO_2), 20.6 (CH_2CH_3), 14.6 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1741 (C=O, ester), 1594 (C=O, vinylogous amide) cm^{-1}. MS (70 eV): *m*/*z* (%) = 403 [M^+ + H] (8), 402 [M^+] (32), 273 (39), 272 (17), 168 (15), 131 (8), 130 (100). $C_{25}H_{26}N_2O_3$ calcd 402.1943, found 402.1919 (MS). $[\alpha]_D^{20}$ = −120.6 (*c* = 1, CH_2Cl_2).

(6*RS*)-*N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-6-(4′-chlorphenyl)-3-ethyl-4-oxo-2,3-didehydropiperidine (18c and 19c): colorless amorphous solid, yield: 38%, R_f: 0.46 (hexane/acetone 1:1 (*v*:*v*)). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.15 (brs, 1H, N-H), 7.40 (d, $J_{In4-H,In5-H}$ = 8 Hz, 1H, In 4-H), 7.27 (s, 1H, 2-H), 7.23 (t, $J_{In6-H,In5-H}$ = $J_{In6-H,In7-H}$ = 8 Hz, 1H, In 6-H), 7.15 (d, $J_{In7-H,In6-H}$ = 8 Hz, 1H, In 7-H), 7.04 (t, $J_{In5-H,In4-H}$ = $J_{In5-H,In6-H}$ = 8 Hz, 1H, In 5-H), 6.98 (d, $J_{In2-H,NH}$ = 2.5 Hz, 1H, In 2-H), 6.93 (d, J_{vic} = 8 Hz, 2H, 2 aryl-H), 6.72 (d, J_{vic} = 8 Hz, 2H, 2 aryl-H), 4.54 (dd, $J_{6-H,5-Ha}$ = 13 Hz, $J_{6-H,5-Hb}$ = 5 Hz, 1H, 6-H), 3.84 (dd, J_{vic} = 9 Hz, $J_{vic'}$ = 6 Hz, 1H, CH_2CHCO_2), 3.69 (s, 3H, OCH_3), 3.40 (dd, J_{gem} = 15 Hz, $J_{vic'}$ = 6 Hz, 1H, $CH_{2a}CHCO_2$), 3.14 (dd, J_{gem} = 15 Hz, J_{vic} = 9 Hz, 1H, $CH_{2b}CHCO_2$), 2.56 (dd, J_{gem} = 16 Hz, $J_{5-Ha,6-H}$ = 13 Hz, 1H, 5-Ha), 2.51 (dd, J_{gem} = 16 Hz, $J_{5-Hb,6-H}$ = 5 Hz, 1H, 5-Hb), 2.25 (q, J_{vic} = 8 Hz, 1H, $CH_{2a}CH_3$), 2.24 (q, J_{vic} = 8 Hz, 1H, $CH_{2b}CH_3$), 1.05 (t, J_{vic} = 8 Hz, CH_2CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 190.5 (C-4), 171.4 (CO_2Me), 148.2 (C-2), 136.5 (Ph C-*ipso*), 136.1 (In C-7a), 134.0 (C-*para*), 128.8 (2 aryl C), 128.6 (2 aryl C), 126.9 (In C-3a), 123.2 (In C-2), 122.3 (In C-6), 119.6 (In C-5), 118.1 (In C-4), 114.8 (C-3), 111.3 (In C-7), 110.0 (In C-3), 63.4 (CH_2CHCO_2), 61.4 (C-6), 52.3 (OCH_3), 44.6 (C-5), 26.7 (CH_2CHCO_2), 20.6 (CH_2CH_3), 14.5 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1598 (C=O, vinylogous amide) cm^{-1}. MS (70 eV): *m*/*z* (%) = 438 [MClb$^+$] (5), 436 [M^+] (15), 307 (9), 168 (6), 131 (9), 130 (100). $C_{25}H_{25}N_2O_3Cl$ calcd 436.1554, found 436.1536 (MS). Calcd C 68.72, H 5.77, N 6.41; found: C 68.72, H 6.01, N 6.35. $[\alpha]_D^{20}$ = −97.6 (*c* = 1.15, CH_2Cl_2). (6*S*):(6*R*) = 93:7 (NMR).

(6*RS*)-*N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-3-ethyl-6-(4′-nitrophenyl)-4-oxo-2,3-didehydropiperidine (18d and 19d): yellowish amorphous solid, yield: 35%, R_f: 0.18 (hexane/acetone 1:1 (*v*:*v*)). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.08 (brs, 1H, N-H), 7.67 (d, J_{vic} = 8.5 Hz, 2H, aryl-H), 7.40 (d, $J_{In4-H,In5-H}$ = 8 Hz, 1H, In 4-H), 7.24 (s, 1H, 2-H), 7.20 (t, $J_{In6-H,In5-H}$ = $J_{In6-H,In7-H}$ = 8 Hz, 1H, In 6-H), 7.13 (d, $J_{In7-H,In6-H}$ = 8 Hz, 1H, In 7-H), 6.99 (d, $J_{In2-H,NH}$ = 2.5 Hz, 1H, In 2-H), 6.94 (t, $J_{In5-H,In4-H}$ = $J_{In5-H,In6-H}$ = 8 Hz, 1H, In 5-H), 6.83 (d, J_{vic} = 8.5 Hz, 2H, aryl-H), 4.64 (dd, $J_{6-H,5-Hb}$ = 12 Hz, $J_{6-H,5-Ha}$ = 6 Hz, 1H, 6-H), 3.80 (dd, J_{vic} = 10 Hz, $J_{vic'}$ = 5 Hz, 1H, CH_2CHCO_2), 3.74 (s, 3H, OCH_3), 3.41 (dd, J_{gem} = 16 Hz, J_{vic} = 5 Hz, 1H, $CH_{2a}CHCO_2$), 3.19 (dd, J_{gem} = 16 Hz, J_{vic} = 10 Hz, 1H, $CH_{2b}CHCO_2$), 2.60 (dd, J_{gem} = 16 Hz, $J_{5-Ha,6-H}$ = 6 Hz, 1H, 5-Ha), 2.51 (dd, J_{gem} = 16 Hz, $J_{5-Hb,6-H}$ = 12 Hz, 1H, 5-Hb), 2.25 (q, J_{vic} = 8 Hz, 2H, CH_2CH_3), 1.04 (t, J_{vic} = 8 Hz, CH_2CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 189.4 (C-4), 171.1 (CO_2Me), 147.7 (C-2), 147.3 (C-*ipso*), 145.3 (C-*para*), 136.1 (In C-7a), 127.7 (2 aryl C), 126.6 (In C-3a), 123.5 (2 aryl C), 123.3 (In C-2), 122.3 (In C-6), 119.4 (In C-5), 117.7 (In C-4), 114.5 (C-3), 111.4 (In C-7), 109.5 (In C-3), 62.9 (CH_2CHCO_2), 62.2 (C-6), 52.4 (OCH_3), 43.8 (C-5), 27.1 (CH_2CHCO_2), 20.5 (CH_2CH_3), 14.4 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1596 (C=O, vinylogous amide) cm^{-1}. MS (70 eV): *m*/*z* (%) = 447 [M^+] (8), 362 (2), 314 (3), 131 (10), 130 (100). $C_{25}H_{25}N_3O_5$ calcd 447.1794, found 447.1784 (MS). $C_{25}H_{25}N_3O_5$ calcd: C 67.10, H 5.63, N 9.39; found: C 66.86, H 5.73, N 9.24. $[\alpha]_D^{20}$ = −155.3 (*c* = 1, CH_2Cl_2, (6*S*):(6*R*) = 94:6 (NMR)).

18e and 19e: The boric acid triphenyl ester was dissolved in dichloromethane (30 mL), cooled to −78 °C and the diene and the imine in dichloromethane (5 mL) were added. The workup was as described above. Yellowish oil, yield: 31%, R_f: 0.25 (hexane/acetone 2:1 (*v*:*v*)). $C_{26}H_{36}N_2O_3$ calcd: C 73.55, H 8.55, N 6.60; found: C 72.93, H 8.50, N 6.38. The diastereomers were separated by MPLC on silica gel using dichloromethane/ethanol 1000:5 (*v*:*v*) as eluent.

(6*R*)-*N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-3-ethyl-6-heptyl-4-oxo-2,3-didehydropiperidine (18e): ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.13 (brs, 1H, N-H), 7.58 (d, $J_{In4-H,In5-H}$ = 8 Hz, 1H, In 4-H), 7.38 (d, $J_{In7-H,In6-H}$ = 8 Hz, 1H, In 7-H), 7.22 (td, $J_{In6-H,In5-H}$ = $J_{In6-H,In7-H}$ = 8 Hz, J = 1 Hz, 1H, In 6-H), 7.15 (td, $J_{In5-H,In4-H}$ = $J_{In5-H,In6-H}$ = 8 Hz, J = 1 Hz, 1H, In 5-H), 7.05 (s, 1H, 2-H), 7.02 (d, $J_{In2-H,NH}$ = 2.5 Hz, 1H, In 2-H), 4.14 (t, J_{vic} = 8 Hz, 1H, CH_2CHCO_2), 3.73 (s, 3H, OCH_3), 3.52 (dd, J_{gem} = 15 Hz, J_{vic} = 8 Hz, 1H, $CH_{2a}CHCO_2$), 3.44–3.36 (m, 1H, 6-H), 3.22 (dd, J_{gem} = 15 Hz, J_{vic} = 8 Hz, 1H, $CH_{2b}CHCO_2$), 2.66 (dd, J_{gem} = 17 Hz, J_{vic} = 7 Hz, 1H, 5-Ha), 2.26 (dd, J_{gem} = 17 Hz, $J_{5-Hb,6-H}$ = 5 Hz, 1H, 5-Hb), 2.22–2.06 (m, 2H, CH_2CH_3), 1.30–0.98 (m, 12H, heptyl-CH_2), 0.98 (t, J_{vic} = 7 Hz, 3H, CH_2CH_3), 0.86 (t, J_{vic} = 7 Hz, 3H, heptyl-CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 190.6 (C-4), 171.8 (CO_2Me), 146.5 (C-2), 136.4 (In C-7a), 126.9 (In C-3a), 123.3 (In C-2), 122.3 (In C-6), 119.7 (In C-5), 118.0 (In C-4), 111.7 (In C-3), 111.6 (In C-7), 109.8 (C-3), 64.4 (CH_2CHCO_2), 58.3 (C-6), 52.5 (OCH_3), 39.7 (C-5), 31.8, 29.6, 29.5, 29.0, 26.9, 25.2, 22.6, 20.5 (CH_2CHCO_2, CH_2CH_3, heptyl-CH_2), 14.6, 14.1 (CH_2CH_3, heptyl-CH_3). IR (film/KBr): $\tilde{\nu}_{max}$ = 1589 (C=O, vinylogous amide) cm^{-1}. MS (70 eV): *m*/*z* (%) = 425 [M^+ + H] (6), 424 [M^+] (22), 365 (4), 295 (14), 294 (14), 197 (9), 196 (35), 131 (9), 130 (100). $C_{26}H_{36}N_2O_3$ calcd 424.2726, found 424.2714 (MS). $[\alpha]_D^{20}$ = −204.1 (*c* = 1, CH_2Cl_2).

(6*S*)-*N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-3-ethyl-6-heptyl-4-oxo-2,3-didehydropiperidine (19e): ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.73 (brs, 1H, N-H), 7.51 (d, $J_{In4-H,In5-H}$ = 8 Hz, 1H, In 4-H), 7.30 (d, $J_{In7-H,In6-H}$ = 8 Hz, 1H, In 7-H), 7.12 (td, $J_{In6-H,In5-H}$ = $J_{In6-H,In7-H}$ = 8 Hz, J = 1 Hz,

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1H, In 6-H), 7.07 (s, 1H, 2-H), 7.03 (td, $J_{In5-H,In4-H} = J_{In5-H,In6-H} = 8$ Hz, $J = 1$ Hz, 1H, In 5-H), 6.93 (d, $J_{In2-H,NH} = 2.5$ Hz, 1H, In 2-H), 4.07 (dd, $J_{vic} = 10$ Hz, $J_{vic'} = 5.3$ Hz, 1H, CH_2CHCO_2), 3.71 (s, 3H, OCH_3), 3.40 (dd, $J_{gem} = 15$ Hz, $J_{vic'} = 5.3$ Hz, 1H, $CH_{2a}CHCO_2$), 3.07 (dd, $J_{gem} = 15$ Hz, $J_{vic} = 10$ Hz, 1H, $CH_{2b}CHCO_2$), 2.79 (m, 1H, 6-H), 2.30–2.01 (m, 3H, 5-Ha, CH_2CH_3), 1.96 (dd, $J_{gem} = 16$ Hz, $J_{5-Hb,6-H} = 2.3$ Hz, 1H, 5-Hb), 1.5–1.0 (m, 12H, heptyl-CH_2), 0.95 (t, $J_{vic} = 7$ Hz, 3H, CH_2CH_3), 0.77 (t, $J_{vic} = 7$ Hz, 3H, heptyl-CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 190.2$ (C-4), 171.8 (CO_2Me), 146.6 (C-2), 136.3 (In C-7a), 126.7 (In C-3a), 123.3 (In C-2), 122.4 (In C-6), 119.8 (In C-5), 118.1 (In C-4), 111.6 (In C-7, In C-3), 110.2 (C-3), 65.7 (CH_2CHCO_2), 60.9 (C-6), 52.5 (OCH_3), 39.5 (C-5), 31.7, 29.8, 29.6, 29.1, 26.8, 25.5, 22.6, 20.4 (CH_2CHCO_2, CH_2CH_3, heptyl-CH_2), 14.6, 14.1 (CH_2CH_3, heptyl-CH_3). IR (film/KBr): $\tilde{\nu}_{max} = 1591$ (C=O, vinylogous amide) cm^{-1}. MS (70 eV): m/z (%) = 425 [M^+ + H] (7), 424 [M^+] (27), 294 (19), 207 (11), 197 (13), 196 (40), 149 (10), 131 (9), 130 (100), 124 (9), 113 (64), 71 (11), 69 (9), 57 (18), 55 (20), 43 (26), 41 (11). $C_{26}H_{36}N_2O_3$ calcd 424.2726, found 424.2714 (MS). $[\alpha]_D^{20} = +40.3$ ($c = 0.4$, CH_2Cl_2).

(6*RS*)-*N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-3-ethyl-4-oxo-6-(2′-propyl)-2,3-didehydropiperidine (18f and 19f): yellowish oil, yield: 29%, R_f: 0.12 (hexane/acetone 2:1 (v:v)). ^{1}H NMR (400 MHz, $CDCl_3$): $\delta = 8.21$ (brs, 1H, N-H), 7.58 (d, $J_{In4-H,In5-H} = 8$ Hz, 1H, In 4-H), 7.38 (d, $J_{In7-H,In6-H} = 8$ Hz, 1H, In 7-H), 7.22 (td, $J_{In6-H,In5-H} = J_{In6-H,In7-H} = 8$ Hz, $J = 1$ Hz, 1H, In 6-H), 7.18 (s, 1H, 2-H), 7.15 (td, $J_{In5-H,In4-H} = J_{In5-H,In6-H} = 8$ Hz, $J = 1$ Hz, 1H, In 5-H), 7.05 (d, $J_{In2-H,NH} = 2.5$ Hz, 1H, In 2-H), 4.16 (t, $J_{vic} = 8$ Hz, 1H, CH_2CHCO_2), 3.71 (s, 3H, OCH_3), 3.57 (dd, $J_{gem} = 15$ Hz, $J_{vic} = 8$ Hz, 1H, $CH_{2a}CHCO_2$), 3.26 (dd, $J_{gem} = 15$ Hz, $J_{vic} = 8$ Hz, 1H, $CH_{2b}CHCO_2$), 3.22 (ddd, $J_{6-H,CH(CH3)2} = 10$ Hz, $J_{6-H,5-Ha} = 7$ Hz, $J_{6-H,5-Hb} = 5$ Hz, 1H, 6-H), 2.63 (dd, $J_{gem} = 17$ Hz, $J_{5-Ha,6-H} = 7$ Hz, 1H, 5-Ha), 2.36 (dd, $J_{gem} = 17$ Hz, $J_{5-Hb,6-H} = 5$ Hz, 1H, 5-Hb), 2.22 (dq, $J_{gem} = 16$ Hz, $J_{vic} = 8$ Hz, 1H, $CH_{2a}CH_3$), 2.10(dq, $J_{gem} = 16$ Hz, $J_{vic} = 8$ Hz, 1H, $CH_{2b}CH_3$), 1.90–1.80 (m, 1H, $CH(CH_3)_2$), 1.01 (t, $J_{vic} = 8$ Hz, 3H, CH_2CH_3), 0.81 (d, $J_{vic} = 8$ Hz, 3H, $CH(CH_3)_{2a}$), 0.64 (d, $J_{vic} = 8$ Hz, 3H, $CH(CH_3)_{2b}$). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 191.0$ (C-4), 172.0 (CO_2Me), 146.7 (C-2), 136.3 (In C-7a), 126.8 (In C-3a), 123.3 (In C-2), 122.2 (In C-6), 119.6 (In C-5), 117.9 (In C-4), 111.9 (C-3), 111.6 (In C-7), 109.4 (In C-3), 64.3 (CH_2CHCO_2), 63.6 (C-6), 52.4 (OCH_3), 36.0 (C-5), 30.0 ($CH(CH_3)_2$), 27.2 (CH_2CHCO_2), 20.6 (CH_2CH_3), 19.3 ($CH(CH_3)_2$), 17.0 ($CH(CH_3)_2$), 14.5 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max} = 1591$ (C=O, vinylogous amide) cm^{-1}. MS (70 eV): m/z (%) = 369 [M^+ + H] (7), 368 [M^+] (33), 325 (7), 239 (26), 238 (22), 196 (11), 131 (9), 130 (100). $C_{22}H_{28}N_2O_3$ calcd 368.2100, found 368.2113 (MS). Calcd C 71.71, H 7.66, N 7.60; found: C 71.34, H 7.60, N 7.69. $[\alpha]_D^{20} = -187.1$ ($c = 0.7$, CH_2Cl_2, (6*S*):(6*R*) > 98:2 (NMR)).

Transformations using the chiral catalysts 20 and 21: Powdered molecular sieves 4 Å (0.3 g) and the enantiomerically pure binaphthol (0.057 g, 0.2 mmol) were suspended in dichloromethane (7 mL), a 1 M solution of boric acid triphenyl ester (0.2 mL, 0.2 mmol) was added, the mixture was stirred for 1 h at room temperature and then cooled to 0 °C. A solution of the imine (0.2 mmol) in dichloromethane (1 mL) was added and after stirring for 15 min, the mixture was cooled to the reaction temperature (Table 1) and the diene **13** (0.08 g, 0.32 mmol, 1.6 equiv) was added. The workup was as described above.

(6*S*)-*N*-(2-[Indol-3-yl]ethyl)-3-ethyl-4-oxo-6-phenyl-2,3-didehydropiperidine (18g) and (6*R*)-*N*-(2-[indol-3-yl]ethyl)-3-ethyl-4-oxo-6-phenyl-2,3-didehydropiperidine (19g): colorless crystals, m.p. 171 °C (hexane/acetone), R_f: 0.35 (hexane/acetone 2:1 (v:v)). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 8.55$ (brs, 1H, N-H), 7.40–7.20 (m, 7H, 5 Ph-H, In 4-H, In 7-H), 7.15 (t, $J_{In6-H,In5-H} = J_{In6-H,In7-H} = 8$ Hz, 1H, In 6-H), 7.05 (t, $J_{In5-H,In4-H} = J_{In5-H,In6-H} = 8$ Hz, 1H, In 5-H), 6.90 (d, $J_{In2-H,NH} = 2.5$ Hz, 1H, In 2-H), 6.80 (s, 1H, 2-H), 4.53 (t, $J_{6-H,5-Hb} = J_{6-H,5-Ha} = 8$ Hz, 1H, 6-H), 3.33 (t, $J_{vic} = 7$ Hz, 2H, InCH_2CH_2N), 3.00–2.80 (m, 2H, InCH_2CH_2N), 2.70–2.60 (m, 2H, 5-Ha, 5-Hb), 2.05 (q, $J_{vic} = 7$ Hz, 2H, CH_2CH_3), 0.87 (t, $J_{vic} = 7$ Hz, CH_2CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 189.2$ (C-4), 152.4 (C-2), 138.9 (Ph C-*ipso*), 136.2 (In C-7a), 128.7 (2 Ph C), 127.9 (Ph C-*para*), 127.0 (2 Ph C), 126.7 (In C-3a), 122.5 (In C-2), 121.7 (In C-6), 119.1 (In C-5), 118.0 (In C-4), 111.4 (In C-7), 111.3 (In C-3), 111.2 (C-3), 61.4 (C-6), 53.4 (InCH_2CH_2N), 44.0 (C-5), 24.8 (CH_2CHCO_2), 20.0 (CH_2CH_3), 14.1 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max} = 1572$ (C=O, vinylogous amide) cm^{-1}. MS (70 eV): m/z (%) = 345 [M^+ + H] (13), 344 [M^+] (58), 215 (31), 214 (100), 130 (21), 117 (12), 110 (54). $C_{23}H_{24}N_2O_3$ calcd 344.1889, found 344.1877 (MS). Calcd C 80.20, H 7.07, N 8.13; found: C 79.93, H 7.03, N 8.19.
(6*S*)-Enantiomer **18g**: $[\alpha]_D^{20} = -127.7$ ($c = 0.3$, CH_2Cl_2). The enantiomeric ratio was determined by analytical HPLC using a column ZWE 376A [20] (kindly supplied by Bayer) and THF/hexane 60:40 (v:v) as eluent, flow: 1 mL min^{-1}. (6*S*)-Enantiomer **18g**: R_t: 4.14 min, (6*R*)-enantiomer **19g**: R_t: 8.19 min.

Preparation of N^{ind}-formyl tryptophan methyl ester hydrochloride (22): A solution of L-tryptophan methyl ester hydrochloride (30 g, 0.118 mol) in formic acid (100 mL) was saturated with hydrogen chloride (30 min). The deep violet solution was allowed to stand for 2 h at room temperature in a pressure-resistant bottle. After evaporation of the solvent in vacuo, the remaining residue was recrystallized from ethanol/ethyl acetate, yielding 32.5 g (97%) of the protected indole. Colorless crystals, yield: 97%, m.p. 176 °C (decomp.). ^{1}H NMR (250 MHz, D_2O): $\delta = 9.19$ (brs, 0.38H, CHO), 8.86 (brs, 0.62H, CHO), 8.08 (brs, 0.62H, In 7-H), 7.62 (brs, 0.38H, In 7-H), 7.58–7.26 (m, 4H, In 2-H, In 4-H, In 5-H, In 6-H), 4.42 (t, $J_{vic} = 7.5$ Hz, 1H, CH_2CHCO_2), 3.78 (s, 3H, OCH_3), 3.40–3.20 (m, 2H, CH_2CHCO_2). ^{13}C NMR (100.6 MHz, D_2O): $\delta = 171.0$ (CO_2Me), 163.2, 159.9 (CHO), 136.2, 134.7 (In C-7a), 131.2, 130.4 (In C-3a), 127.0, 126.6 (In C-6), 126.8, 125.6 (In C-5), 126.1, 121.8 (In C-2), 120.3, 119.8 (In C-4), 118.2 (In C-3), 116.7, 111.7 (In C-7), 54.8 (OCH_3), 53.5 (CH_2CHCO_2), 26.4 (CH_2CHCO_2). IR (drift): $\tilde{\nu}_{max} = 1738$ (C=O, ester) cm^{-1}. MS (70 eV): m/z (%) = 246 [M^+ − HCl] (26), 159 (41), 158 (62), 130 (100), 88 (24), 77 (10). $C_{13}H_{14}N_2O_3^+$ calcd 246.1004, found 246.0989 [M^+ − HCl] (MS). $C_{13}H_{14}N_2O_3 \cdot$HCl calcd: C 55.23, H 5.35, N 9.91; found: C 55.27, H 5.28, N 9.78. $[\alpha]_D^{20} = +12.7$ ($c = 2$, MeOH).

General procedure for the reaction of the formaldeyde imine 24 with the dienes 13 and 16 in aqueous THF: A solution of N^{ind}-formyl tryptophan methyl ester hydrochloride **22** (0.5 g, 1.76 mmol) in water (5 mL) was treated with a saturated $NaHCO_3$ solution (2 mL) and extracted 4 times with dichloromethane (25 mL). To the combined organic phases was added a 37% formaldehyde solution in water (0.143 g, 1.76 mmol) and $MgSO_4$ (5 g) under vigorous stirring. After 1 h at room temperature the solid was removed by filtration, washed with dichloromethane and the solvent was removed in vacuo. The crude imine was dried for 30 min in vacuo and was used in the following procedure without further purification.
The Schiff base was dissolved in THF (90 mL) and water (10 mL), $LiClO_4$ (1.80 g, 17 mmol, 10 equiv), and the diene **16** (0.5 g, 2.9 mmol, 1.7 equiv) or the diene **13** (0.6 g, 2.4 mmol, 1.4 equiv) was added. After stirring at room temperature for 3 d, the mixture was concentrated in vacuo, and water (50 mL) was added to the residue. The aqueous phase was extracted 4 times with dichloromethane (50 mL). The combined organic layers were dried with $MgSO_4$ and the solvent was removed in vacuo. The product was isolated from the remaining residue by flash chromatography using hexane/acetone mixtures as eluents.

***N*-((*S*)-1-Carboxymethyl-2-[N^{ind}-formylindol-3-yl]ethyl)-4-oxo-2,3-didehydropiperidine (25)**: yellowish oil, yield 45%, R_f: 0.19 (hexane/acetone 1:1 (v:v)). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 9.38$ (brs, 0.36H, CHO), 9.08 (brs, 0.64H, CHO), 8.40 (brs, 0.64H, In 7-H), 7.70 (brs, 0.36H, In 7-H), 7.65–7.20 (m, 4H, In 2-H, In 4-H, In 5-H, In 6-H), 6.98 (d, $J_{2-H,3-H} = 7.5$ Hz, 1H, 2-H), 4.93 (d, $J_{3-H,2-H} = 7.5$ Hz, 1H, 3-H), 4.22 (dd, $J_{vic} = 10$ Hz, $J_{vic'} = 6$ Hz, 1H, CH_2CHCO_2), 3.78 (s, 3H, OCH_3), 3.62–3.35 (m, 3H, 6-Ha, 6-Hb, $CH_{2a}CHCO_2$), 3.20 (dd, $J_{gem} = 15$ Hz, $J_{vic} = 10$ Hz, 1H, $CH_{2b}CHCO_2$), 2.50–2.30 (m, 2H, 5-Ha, 5-Hb). ^{13}C NMR (62.9 MHz, $CDCl_3$): $\delta = 191.8$ (C-4), 170.2 (CO_2Me), 159.1, 155.7 (CHO), 152.6 (C-2), 135.2, 134.4 (In C-7a), 130.2, 130.0 (In C-3a), 125.9, 125.3 (In C-6), 124.8, 124.2 (In C-5), 123.5, 120.1 (In C-2), 119.3, 118.3 (In C-4), 118.8, 117.9 (In C-3), 116.5, 110.0 (In C-7), 100.3 (C-3), 65.9 (CH_2CHCO_2), 52.9 (OCH_3), 45.6 (C-6), 37.7 (C-5), 25.8 (CH_2CHCO_2). IR (film/KBr): $\tilde{\nu}_{max} = 1707$ (C=O, ester) cm^{-1}. MS (70 eV): m/z (%) = 326 [M^+] (38), 168 (100), 158 (39), 130 (53). $C_{18}H_{18}N_2O_4$ calcd 326.1267, found 326.1246 (MS). Calcd C 66.25, H 5.56, N 8.58; found: C 66.39, H 5.73, N 8.82. $[\alpha]_D^{20} = -131.5$ ($c = 1$, CH_2Cl_2).

***N*-((*S*)-1-Carboxymethyl-2-[N^{ind}-formylindol-3-yl]ethyl)-3-ethyl-4-oxo-2,3-didehydropiperidine (26)**: yellowish oil, yield: 62%, R_f: 0.15 (hexane/acetone 3:2 (v:v)). ^{1}H NMR (250 MHz, $CDCl_3$): $\delta = 9.40$ (brs, 0.4H, CHO), 9.05 (brs, 0.6H, CHO), 8.40 (brs, 0.6H, In 7-H), 7.71 (brs, 0.4H, In 7-H), 7.65–7.20 (m, 4H, In 2-H, In 4-H, In 5-H, In 6-H), 6.82 (s, 1H, 2-H), 4.18

(dd, J_{vic} = 9 Hz, $J_{vic'}$ = 6 Hz, 1H, CH_2CHCO_2), 3.78 (s, 3H, OCH_3), 3.58–3.32 (m, 3H, $CH_{2a}CHCO_2$, 6-Ha, 6-Hb), 3.17 (dd, J_{gem} = 15 Hz, J_{vic} = 9 Hz, 1H, $CH_{2b}CHCO_2$), 2.55-2.30 (m, 2H, 5-Ha, 5-Hb), 2.18–2.00 (m, 2H, CH_2CH_3), 0.90 (t, J_{vic} = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 191.1 (C-4), 170.4 (CO_2Me), 159.0, 155.6 (CHO), 149.9 (C-2), 135.2, 134.3 (In C-7a), 130.4, 130.1 (In C-3a), 125.7, 125.1 (In C-6), 124.7, 124.1 (In C-5), 123.4, 120.0 (In C-2), 119.4, 118.4 (In C-4), 119.0, 118.2 (In C-3), 116.4, 109.9 (In C-7), 113.9 (C-3), 65.8 (CH_2CHCO_2), 52.6 (OCH_3), 45.8 (C-6), 36.0 (C-5), 25.6 (CH_2CH_3), 20.3 (CH_2CHCO_2), 14.3 (CH_2CH_3). IR (film/KBr): $\tilde{\nu}_{max}$ = 1707 (C=O, ester), 1599 (C=O, vinylogous amide) cm^{-1}. MS (70 eV): *m/z* (%) = 355 [M^+ + H] (4), 354 [M^+] (34), 197 (19), 196 (100), 130 (27). $C_{20}H_{22}N_2O_4$ calcd 354.1580, found: 354.1549 (MS). Calcd C 67.78, H 6.26, N 7.90; found: C 67.25, H 6.16, N 7.91. $[\alpha]_D^{20}$ = −139.7 (*c* = 1, CH_2Cl_2).

Removal of the formamide from 25 and 26: The formyl-protected cnaminones were dissolved in a mixture of methanol (40 mL) and water (10 mL). To this solution a 1 M Na_2HPO_4 solution (5 mL) was added. The mixture was stirred for 2 d at room temperature and concentrated in vacuo. The remainig residue was diluted with water (20 mL), the pH was adjusted to 2 with 1 M hydrochloric acid and extracted 4 times with dichloromethane (30 mL). The combined organic phases were dried with K_2CO_3 and the solvent was removed in vacuo.

***N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-4-oxo-2,3-didehydropiperidine (27)**: All analytical data were consistent with literature values: see ref. [5].

***N*-((*S*)-1-Carboxymethyl-2-[indol-3-yl]ethyl)-3-ethyl-4-oxo-2,3-didehydropiperidine (28)**: Colorless crystals, yield: 93%, m.p. 163 °C (hexane/acetone), R_f: 0.15 (hexane/acetone 3:2 (*v*:*v*)). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 8.77 (brs, 1H, N-H), 7.60 (d, $J_{In4-H,In5-H}$ = 8 Hz, 1H, In 4-H), 7.39 (d, $J_{In7-H,In6-H}$ = 8 Hz, 1H, In 7-H), 7.20 (td, $J_{In6-H,In5-H} = J_{In6-H,In7-H}$ = 8 Hz, *J* = 1 Hz, 1H, In 6-H), 7.12 (td, $J_{In5-H,In4-H} = J_{In5-H,In6-H}$ = 8 Hz, *J* = 1 Hz, 1H, In 5-H), 7.00 (d, $J_{In2-H,NH}$ = 2.5 Hz, 1H, In 2-H), 6.77 (s, 1H, 2-H), 4.20 (dd, J_{vic} = 11 Hz, $J_{vic'}$ = 6 Hz, 1H, CH_2CHCO_2), 3.77 (s, 3H, OCH_3), 3.52–3.30 (m, 3H, $CH_{2a}CHCO_2$, 6-Ha, 6-Hb), 3.20 (dd, J_{gem} = 15 Hz, J_{vic} = 11 Hz, 1H, $CH_{2b}CHCO_2$), 2.50–2.25 (m, 2H, 5-Ha, 5-Hb), 2.03 (q, J_{vic} = 7 Hz, 2H, CH_2CH_3), 0.83 (t, J_{vic} = 7 Hz, CH_2CH_3). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 191.4 (C-4), 171.2 (CO_2Me), 151.1 (C-2), 136.4 (In C-7a), 126.8 (In C-3a), 123.4 (In C-2), 122.3 (In C-6), 119.7 (In C-5), 118.1 (In C-4), 112.9 (C-3), 111.8 (In C-7), 109.9 (In C-3), 66.9 (CH_2CHCO_2), 52.6 (OCH_3), 46.0 (C-6), 36.1 (C-5), 26.3 (CH_2CHCO_2), 20.4 (CH_2CH_3), 14.5 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1728 (C=O, ester), 1568 (C=O, vinylogous amide) cm^{-1}. MS (70 eV): *m/z* (%) = 326 (21), 197 (12), 196 (12), 130 (100). $C_{19}H_{22}N_2O_3$ calcd 326.1630, found 326.1611 (MS). Calcd C 69.92, H 6.79, N 8.58; found: C 69.84, H 6.75, N 8.58. $[\alpha]_D^{20}$ = −185 (*c* = 1, CH_2Cl_2).

Preparation of the indolo[2,3-*a*]quinolizines 32 and 33 by condensation of the enaminones 18 with phosgene: To a solution of the enaminone **18** (1 mmol) in dichloromethane (10 mL) under nitrogen a 1.93 M solution of phosgene in toluene (0.57 mL, 1.1 mmol, 1.1 equiv) was added. The color quickly turned to deep red and black. After being stirred overnight at room temperature, the solvent was removed in vacuo, and the remaining residue was treated with water (5 mL) and a saturated solution of Na_2CO_3 (2 mL). The mixture was extracted 3 times with dichloromethane (20 mL). The combined organic phases were dried with $MgSO_4$ and the solvent was evaporated. The products were isolated from the remaining residue by flash chromatography on silica gel using hexane/ethyl acetate mixtures as eluents.

(6*S*,12b*R*)-6-Carboxymethyl-2-chloro-3,4,5,6,7,12b-hexahydroindolo[2,3-*a*]-quinolizine (32a): colorless amorphous substance, yield: 36%, R_f: 0.15 (hexane/ethyl acetate 4:1 (*v*:*v*)). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 8.10 (brs, 1H, 12-H), 7.45 (dd, $J_{8-H,9-H}$ = 8 Hz, *J* = 1.5 Hz, 1H, 8-H), 7.23 (dd, $J_{11-H,10-H}$ = 8 Hz, *J* = 1.5 Hz, 1H, 11-H), 7.18–7.02 (m, 2H, 9-H, 10-H), 6.05 (brs, 1H, 1-H), 5.00 (brs, 1H, 12b-H), 3.95 (t, J_{vic} = 4 Hz, 1H, 6-H), 3.65 (s, 3H, OCH_3), 3.27–3.13 (m, 3H, 4-Ha, 7-Ha, 7-Hb), 3.07 (dt, J_{gem} = 14 Hz, $J_{4-Hb,3-H}$ = 5 Hz, 1H, 4-Hb), 2.62–2.37 (m, 2H, 3-Ha, 3-Hb). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 172.9 (CO_2Me), 136.3 (C-11a), 132.1 (C-12a), 131.7 (C-8a), 127.0 (C-2), 122.7 (C-1), 121.9 (C-10), 119.6 (C-9), 118.2 (C-8), 111.0 (C-11), 105.6 (C-7a), 60.6 (C-6), 52.1 (C-12b), 52.0 (OCH_3), 48.7 (C-4), 33.2 (C-3), 23.1 (C-7). IR (drift): $\tilde{\nu}_{max}$ = 1731 (C=O, ester) cm^{-1}. MS (70 eV): *m/z* (%) = 318 [*M*Clb$^+$] (14), 317 [*M*Clb$^+$ − H, M^+ + H] (11), 316 [M^+] (47), 282 (15), 281 (100), 257 (46), 255 (26), 221 (29). $C_{17}H_{17}N_2O_2Cl$ calcd 316.0979, found 316.0963 (MS). Calcd C 64.46, H 5.41, N 8.84; found: C 64.04, H 5.62, N 8.51. $[\alpha]_D^{20}$ = +119.6 (*c* = 0.25, CH_2Cl_2).

(6*S*,12b*S*)-6-Carboxymethyl-2-chloro-3,4,5,6,7,12b-hexahydroindolo-[2,3-a]-quinolizine (33a): colorless amorphous substance, yield: 10%, R_f: 0.09 (hexane/ethyl acetate 4:1 (*v*:*v*)). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 8.07 (brs, 1H, 12-H), 7.49 (dd, $J_{8-H,9-H}$ = 8 Hz, *J* = 1.5 Hz, 1H, 8-H), 7.30 (dd, $J_{11-H,10-H}$ = 8 Hz, *J* = 1.5 Hz, 1H, 11-H), 7.18 (td, $J_{10-H,9-H} = J_{10-H,11-H}$ = 8 Hz, *J* = 1 Hz, 1H, 10-H), 7.10 (td, $J_{9-H,8-H} = J_{9-H,10-H}$ = 8 Hz, *J* = 1 Hz, 1H, 9-H), 6.15 (d, *J* = 4 Hz, 1H, 1-H), 4.85 (brs, 1H, 12b-H), 4.00 (dd, J_{vic} = 11 Hz, J_{vic} = 6 Hz, 1H, 6-H), 3.82 (s, 3H, OCH_3), 3.20–2.67 (m, 5H, 3-Ha, 4-Ha, 4-Hb, 7-Ha, 7-Hb), 2.30–2.10 (m, 1H, 3-Hb). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 172.0 (CO_2Me), 136.2 (C-11a), 133.9 (C-12a), 131.8 (C-8a), 126.7 (C-2), 122.1 (C-1), 121.1 (C-10), 119.8 (C-9), 118.3 (C-8), 111.1 (C-11), 106.2 (C-7a), 62.0 (C-6), 56.1 (C-12b), 52.4 (OCH_3), 40.5 (C-4), 33.4 (C-3), 19.8 (C-7). IR (drift): $\tilde{\nu}_{max}$ = 1731 (C=O, ester) cm^{-1}. MS (70 eV): *m/z* (%) = 318 [*M*Clb$^+$] (28), 317 [*M*Clb$^+$ − H, M^+ + H] (25), 316 [M^+] (92), 315 [M^+ − H] (32), 281 (59), 259 (27), 257 (100). $C_{17}H_{17}N_2O_2Cl$ calcd 316.0979, found 316.0989 (MS). Calcd C 64.46, H 5.41, N 8.84; found: C 63.97, H 5.61, N 8.53. $[\alpha]_D^{20}$ = −74.4 (*c* = 0.25, CH_2Cl_2).

(6*S*,12b*R*)-6-Carboxymethyl-2-chloro-1-ethyl-3,4,5,6,7,12b-hexahydroindolo-[2,3-*a*]quinolizine (32b): colorless amorphous substance, yield: 36%, R_f: 0.14 (hexane/ethyl acetate 4:1 (*v*:*v*)). ^{1}H NMR (250 MHz, CDCl$_3$): δ = 8.10 (brs, 1H, 12-H), 7.46 (dd, $J_{8-H,9-H}$ = 8 Hz, *J* = 1.3 Hz, 1H, 8-H), 7.31 (dd, $J_{11-H,10-H}$ = 8 Hz, *J* = 1.3 Hz, 1H, 11-H), 7.12 (td, $J_{10-H,9-H} = J_{10-H,11-H}$ = 8 Hz, *J* = 1.5 Hz, 1H, 10-H), 7.09 (td, $J_{9-H,8-H} = J_{9-H,10-H}$ = 8 Hz, *J* = 1.5 Hz, 1H, 9-H), 5.07 (brs, 1H, 12b-H), 4.01 (dd, J_{vic} = 6 Hz, $J_{vic'}$ = 3 Hz, 1H, 6-H), 3.73 (s, 3H, OCH_3), 3.30–2.95 (m, 3H, 7-Ha, 7-Hb, 4-Ha), 2.92–2.65 (m, 3H, $CH_{2a}CH_3$, 4-Hb, 3-Ha), 2.35–2.17 (m, 2H, 3-Hb, $CH_{2b}CH_3$), 1.14 (t, *J* = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 172.3 (CO_2Me), 136.0 (C-11a), 132.4 (C-12a), 131.4 (C-8a), 128.0 (C-1), 126.6 (C-2), 122.1 (C-10), 119.7 (C-9), 118.2 (C-8), 111.1 (C-11), 105.0 (C-7a), 60.8 (C-6), 53.6 (C-12b), 52.4 (OCH_3), 46.3 (C-4), 33.0 (C-3), 26.1 (CH_2CH_3), 20.2 (C-7), 11.8 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1735 (C=O, ester) cm^{-1}. MS (70 eV): *m/z* (%) = 346 [*M*Clb$^+$] (26), 345 (18), 344 [M^+] (81), 315 (53), 309 (100), 285 (62). $C_{19}H_{21}N_2O_2Cl$ calcd 344.1292, found 344.1279 (MS). Calcd C 66.18, H 6.14, N 8.12; found: C 65.81, H 6.39, N 7.68. $[\alpha]_D^{20}$ = + 57.4 (*c* = 0.35, CH_2Cl_2).

(6*S*,12b*S*)-6-Carboxymethyl-2-chloro-1-ethyl-3,4,5,6,7,12b-hexahydroindolo-[2,3-*a*]quinolizine (33b): colorless amorphous substance, yield: 18%, R_f: 0.23 (hexane/ethyl acetate 4:1 (*v*:*v*)). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.81 (brs, 1H, 12-H), 7.50 (d, $J_{8-H,9-H}$ = 8 Hz, 1H, 8-H), 7.34 (d, $J_{11-H,10-H}$ = 8 Hz, 1H, 11-H), 7.19 (td, $J_{10-H,9-H} = J_{10-H,11-H}$ = 8 Hz, *J* = 1 Hz, 1H, 10-H), 7.10 (td, $J_{9-H,8-H} = J_{9-H,10-H}$ = 8 Hz, *J* = 1 Hz, 1H, 9-H), 4.88 (brs, 1H, 12b-H), 4.17 (dd, J_{vic} = 10 Hz, $J_{vic'}$ = 7 Hz, 1H, 6-H), 3.83 (s, 3H, OCH3), 3.14–3.05 (m, 2H, 7-Ha, 7-Hb), 3.02–2.90 (m, 2H, 4-Ha, $CH_{2a}CH_3$), 2.89–2.76 (m, 2H, 3-Ha, 4-Hb), 2.28–2.15 (m, 2H, $CH_{2b}CH_3$, 3-Hb), 1.30 (t, J_{vic} = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (62.9 MHz, CDCl$_3$): δ = 171.8 (CO_2Me), 135.9 (C-11a), 132.1 (C-12a), 131.7 (C-8a), 129.2 (C-1), 126.5 (C-2), 122.2 (C-10), 119.9 (C-9), 118.2 (C-8), 111.1 (C-11), 106.9 (C-7a), 61.7 (C-6), 58.5 (C-12b), 52.5 (OCH_3), 39.7 (C-4), 33.7 (C-3), 26.3 (CH_2CH_3), 19.7 (C-7), 11.7 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1736 (C=O, ester) cm^{-1}. MS (70 eV): *m/z* (%) = 347 [*M*Clb$^+$ + H] (5), 346 [*M*Clb$^+$] (31), 344 [M^+] (92), 309 (60), 285 (100). $C_{19}H_{21}N_2O_2Cl$ calcd 344.1292, found 344.1302 (MS). Calcd C 66.18, H 6.14, N 8.12; found: C 65.62, H 6.49, N 7.63. $[\alpha]_D^{20}$ = −15.3 (*c* = 0.3, CH_2Cl_2).

(4*S*,6*S*,12b*R*)-6-Carboxymethyl-2-chloro-1-ethyl-4-phenyl-3,4,5,6,7,12b-hexahydroindolo[2,3-*a*]quinolizine (32c): Contains 17% (4*S*,6*S*,12b*S*)-6-carboxymethyl-2-chloro-1-ethyl-4-phenyl-1,4,5,6,7,12b-hexahydroindolo[2,3-*a*]-quinolizine. The two isomers were not separable by chromatography. The ratio was determined from the ^{1}H NMR spectra. Yellowish amorphous solid, yield: 42%, R_f: 0.24 (hexane/ethyl acetate 4:1 (*v*:*v*)). ^{1}H NMR (400 MHz, CDCl$_3$): δ = 7.93 (brs, 1H, 12-H), 7.39 (d, $J_{8-H,9-H}$ = 8 Hz, 1H, 8-H), 7.35–7.18 (m, 6H, Ph-H, 11-H), 7.09 (td, $J_{10-H,9-H} = J_{10-H,11-H}$ = 8 Hz, *J* = 1 Hz, 1H, 10-H), 7.01 (td, $J_{9-H,8-H} = J_{9-H,10-H}$ = 8 Hz, *J* = 1 Hz, 1H, 9-H), 5.19 (brs, 1H, 12b-H), 4.43 (dd, J_{vic} = 10 Hz, $J_{vic'}$ = 4 Hz, 1H, 4-H), 3.76 (dd, $J_{6-H,7-Hb}$ = 6 Hz, $J_{6-H,7-Ha}$ = 2 Hz, 1H, 6-H), 3.39 (s, 3H, OCH_3), 3.05 (dt, J_{gem} = 15 Hz, $J_{7-Ha,6-H}$ = 2 Hz, *J* = 2 Hz, 1H, 7-Ha),

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3.00–2.85 (m, 2H, 3-Ha, 7-Hb), 2.61 (q, J_{vic} = 8 Hz, 2H, CH_2CH_3), 2.52 (ddd, J_{gem} = 15 Hz, $J_{3-Hb,4-H}$ = 4 Hz, J = 2 Hz, 1H, 3-Hb), 1.16 (t, J_{vic} = 8 Hz, 3H, CH_2CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.4 (CO_2Me), 141.2 (Ph C-*ipso*), 136.1 (C-11a), 133.8 (C-12a), 131.9 (C-8a), 128.9 (2Ph C), 128.4 (2Ph C), 128.2 (Ph C-*para*), 128.0 (C-1), 126.9 (C-2), 122.0 (C-10), 119.5 (C-9), 118.2 (C-8), 110.8 (C-11), 109.4 (C-7a), 63.1 (C-4), 57.2 (C-12b), 56.5 (C-6), 51.4 (OCH_3), 43.3 (C-3), 25.0 (C-7), 24.5 (CH_2CH_3), 12.6 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1737 (C=O, ester) cm^{-1}. MS (70 eV): *m/z* (%) = 423 [*M*Clb$^+$ + H] (6), 422 [*M*Clb$^+$] (28), 421 (25), 420 [*M*$^+$] (89), 385 (69), 329 (89), 169 (100). $C_{25}H_{25}N2O_2Cl$ calcd 420.1605, found 420.1614 (MS). $[\alpha]_D^{20}$ = −43 (*c* = 0.6, CH_2Cl_2).

(4*S*,6*S*,12b*S*)-6-Carboxymethyl-2-chloro-1-ethyl-4-phenyl-3,4,5,6,7,12b-hexahydroindolo[2,3-*a*]quinolizine (33c): yellowish amorphous solid, yield: 17%, R_f: 0.46 (hexane/ethyl acetate 4:1 (*v*:*v*)). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (brs, 1H, 12-H), 7.56 (d, $J_{8-H,9-H}$ = 8 Hz, 1H, 8-H), 7.40–7.26 (m, 6H, Ph-H, 11-H), 7.22 (t, $J_{10-H,9-H}$ = $J_{10-H,11-H}$ = 8 Hz, 1H, 10-H), 7.16 (t, $J_{9-H,8-H}$ = $J_{9-H,10-H}$ = 8 Hz, 1H, 9-H), 5.09 (brs, 1H, 12b-H), 4.10 (dd, J_{vic} = 10 Hz, $J_{vic'}$ = 4 Hz, 1H, 4-H), 4.00 (dd, $J_{6-H,7-Ha}$ = 12 Hz, $J_{6-H,7-Hb}$ = 5 Hz, 1H, 6-H), 3.36 (s, 3H, OCH_3), 3.24 (ddd, J_{gem} = 16 Hz, $J_{7-Ha-6-H}$ = 12 Hz, J = 2.5 Hz, 1H, 7-Ha), 2.99 (dq, J_{gem} = 14 Hz, J_{vic} = 7 Hz, 1H, $CH_{2a}CH_3$), 2.95–2.86 (m, 1H, 3-Ha), 2.81 (ddd, J_{gem} = 16 Hz, $J_{7-Hb,6-H}$ = 5 Hz, J = 1.5 Hz, 1H, 7-Hb), 2.38–2.26 (m, 2H, 3-Hb, $CH_{2b}CH_3$), 1.35 (t, J_{vic} = 7 Hz, 3H, CH_2CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 171.4 (CO_2Me), 139.7 (Ph C-*ipso*), 136.1 (C-11a), 132.7 (C-12a), 131.9 (C-8a), 130.3 (2Ph C), 129.0 (Ph C-*para*), 128.5 (C-1), 128.0 (2Ph C), 126.8 (C-2), 122.4 (C-10), 120.1 (C-9), 118.6 (C-8), 111.2 (C-11), 107.9 (C-7a), 62.6 (C-6), 62.2 (C-12b), 57.2 (C-4), 51.8 (OCH_3), 43.4 (C-3), 26.2 (CH_2CH_3), 19.8 (C-7), 11.9 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1736 (C=O, ester) cm^{-1}. MS (70 eV): *m/z* (%) = 423 [*M*Clb$^+$ + H] (7), 422 [*M*Clb$^+$] (32), 421 (31), 420 [*M*$^+$] (100), 361 (90). $C_{25}H_{25}N_2O_2Cl$ calcd 420.1605, found 420.1584 (MS). $[\alpha]_D^{20}$ = −11.8 (*c* = 0.4, CH_2Cl_2).

(4*R*,6*S*,12b*R*)-6-Carboxymethyl-2-chloro-1-ethyl-4-heptyl-3,4,5,6,7,12b-hexahydroindolo[2,3-*a*]quinolizine (32d): Exists in solution as a mixture of *trans* and *cis* conformers. Colorless amorphous substance, yield: 14%, R_f: 0.55 (hexane/ethyl acetate 4:1 (*v*:*v*)).

cis conformer: ^{1}H NMR (250 MHz, $CDCl_3$): δ = 8.45 (brs, 1H, 12-H), 7.42 (d, $J_{8-H,9-H}$ = 8 Hz, 1H, 8-H), 7.30 (d, $J_{11-H,10-H}$ = 8 Hz, 1H, 11-H), 7.10 (td, $J_{10-H,9-H}$ = $J_{10-H,11-H}$ = 8 Hz, J = 1.5 Hz, 1H, 10-H), 7.08 (td, $J_{9-H,8-H}$ = $J_{9-H,10-H}$ = 8 Hz, J = 1.5 Hz, 1H, 9-H), 5.11 (brs, 1H, 12b-H), 4.16 (dd, $J_{6-H,7-Ha}$ = 6 Hz, $J_{6-H,7-Hb}$ = 3 Hz, 1H, 6-H), 3.60 (s, 3H, OCH_3), 3.27 (dd, J_{gem} = 15 Hz, $J_{7-Ha,6-H}$ = 3 Hz, 1H, 7-Ha), 3.10 (dd, J_{gem} = 15 Hz, $J_{7Hb,6-H}$ = 6 Hz, 1H, 7-Hb), 2.65–2.35 (m, 4H, 6-H, 3-Ha, 3-Hb, $CH_{2a}CH_3$), 2.29 (dq, J_{gem} = 14 Hz, J_{vic} = 7 Hz, 1H, $CH_{2b}CH_3$), 1.80–1.00 (m, 15H, heptyl-H, CH_2CH_3), 0.85 (t, J_{vic} = 7 Hz, 3H, heptyl-CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.9 (CO_2Me), 136.1 (C-11a), 134.1 (C-12a), 131.9 (C-8a), 127.6 (C-1), 126.4 (C-2), 121.8 (C-10), 119.4 (C-9), 118.0 (C-8), 111.0 (C-11), 107.9 (C-7a), 58.1 (C-6), 55.2 (C-12b), 53.5 (C-4), 51.8 (OCH_3), 38.7 (C-3), 33.2 (heptyl-C), 31.8 (heptyl-C), 29.7 (heptyl-C), 29.2 (heptyl-C), 26.3 (heptyl-C), 25.3 (CH_2CH_3), 24.1 (heptyl-C), 22.6 (C-7), 14.1 (heptyl-CH_3), 12.3 (CH_2CH_3).

trans conformer: ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.72 (brs, 1H, 12-H), 7.48 (d, $J_{8-H,9-H}$ = 8 Hz, 1H, 8-H), 7.32 (d, $J_{11-H,10-H}$ = 8 Hz, 1H, 11-H), 7.16 (td, $J_{10-H,9-H}$ = $J_{10-H,11-H}$ = 8 Hz, J = 1.5 Hz, 1H, 10-H), 7.11 (td, $J_{9H,8-H}$ = $J_{9-H,10-H}$ = 8 Hz, J = 1.5 Hz, 1H, 9-H), 4.95 (brs, 1H, 12b-H), 4.27 (dd, $J_{6-H,7-Hb}$ = 6 Hz, $J_{6-H,7-Ha}$ = 3.5 Hz, 1H, 6-H), 3.78 (s, 3H, OCH_3), 3.23 (d, J_{gem} = 16 Hz, 1H, 7-Ha), 3.05 (ddd, J_{gem} = 16 Hz, $J_{7-Hb,6-H}$ = 6 Hz, J = 1.5 Hz, 1H, 7-Hb), 2.93 (brs, 1H, 4-H), 2.78 (dq, J_{gem} = 14 Hz, J_{vic} = 7 Hz, 1H, $CH_{2a}CH_3$), 2.47–2.36 (m, 2H, 3-Ha 3-Hb), 2.23 (dq, J_{gem} = 14 Hz, J_{vic} = 7 Hz, 1H, $CH_{2b}CH_3$), 1.60–1.20 (m, 12H, heptyl-H), 1.12 (t, J_{vic} = 7 Hz, 3H, CH_2CH_3), 0.87 (t, J_{vic} = 7 Hz, 3H, heptyl-CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.2 (CO_2Me), 135.8 (C-11a), 134.1 (C-12a), 131.9 (C-8a), 127.3 (C-1), 126.6 (C-2), 122.0 (C-10), 119.6 (C-9), 118.2 (C-8), 111.0 (C-11), 106.3 (C-7a), 59.3 (C-6), 57.0 (C-12b), 53.1 (C-4), 52.4 (OCH_3), 37.3 (C-3), 33.0 (heptyl-C), 31.8 (heptyl-C), 30.7 (heptyl-C), 29.2 (heptyl-C), 26.3 (heptyl-C), 25.5 (CH_2CH_3), 24.1 (heptyl-C), 22.6 (C-7), 14.1 (heptyl-CH_3), 11.9 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1739 (C=O, ester) cm^{-1}. MS (70 Ev) *m/z* (%) = 444 [*M*Clb$^+$] (16), 443 (15), 442 [*M*$^+$] (47), 407 (100), 383 (42), 169 (42). $C_{26}H_{35}N_2O_2Cl$ calcd 442.2387, found 442.2376 (MS). Cacd.: C 70.49, H 7.96, N 6.32; found: C 70.20, H 7.87, N 6.53. $[\alpha]_D^{20}$ = +4 (*c* = 0.35, CH_2Cl_2).

(4*R*,6*S*,12b*S*)-6-Carboxymethyl-2-chloro-1-ethyl-4-heptyl-3,4,5,6,7,12b-hexahydroindolo[2,3-*a*]quinolizine (33d): colorless amorphous substance, yield: 35%, R_f: 0.30 (hexane/ethyl acetate 4:1 (*v*:*v*)). ^{1}H NMR (400 MHz, CDCl3): δ = 7.73 (brs, 1H, 12-H), 7.54 (d, $J_{8-H,9-H}$ = 8 Hz, 1H, 8-H), 7.32 (d, $J_{11-H,10-H}$ = 8 Hz, 1H, 11-H), 7.18 (td, $J_{10-H,9-H}$ = $J_{10-H,11-H}$ = 8 Hz, J = 1.5 Hz, 1H, 10-H), 7.13 (td, $J_{9-H,8-H}$ = $J_{9-H,10-H}$ = 8 Hz, J = 1.5 Hz, 1H, 9-H), 4.93 (brs, 1H, 12b-H), 4.07 (dd, $J_{6-H,7-Ha}$ = 10 Hz, $J_{6-H,7-Hb}$ = 7 Hz, 1H, 6-H), 3.91 (s, 3H, OCH_3), 3.18–3.06 (m, 2H, 7-Ha, 7-Hb), 3.04–2.96 (m, 1H, 4-H), 2.91 (dq, J_{gem} = 14 Hz, J_{vic} = 7 Hz, 1H, $CH_{2a}CH_3$), 2.37–2.28 (m, 2H, 3-Ha, 3-Hb), 2.23 (dq, J_{gem} = 14 Hz, J_{vic} = 7 Hz, 1H, $CH_{2b}CH_3$), 1.55 (m, 1H, heptyl-H), 1.40–1.15 (m, 14H, heptyl-H, CH_2CH_3), 0.85 (t, J_{vic} = 7 Hz, 3H, heptyl-CH_3). ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 173.6 (CO_2Me), 135.8 (C-11a), 132.9 (C-12a), 131.6 (C-8a), 128.7 (C-1), 126.6 (C-2), 122.1 (C-10), 119.9 (C-9), 118.3 (C-8), 111.0 (C-11), 108.1 (C-7a), 61.9 (C-6), 61.5 (C-12b), 52.4 (C-4), 52.3 (OCH_3), 40.1 (C-3), 33.7 (heptyl-C), 31.6 (heptyl-C), 29.6 (heptyl-C), 29.0 (heptyl-C), 26.0 (heptyl-C), 25.9 (CH_2CH_3), 22.6 (heptyl-C), 19.8 (C-7), 14.0 (heptyl-CH_3), 11.7 (CH_2CH_3). IR (drift): $\tilde{\nu}_{max}$ = 1734 (C=O, ester) cm^{-1}. MS (70 eV): *m/z* (%) = 444 [*M*Clb$^+$] (22), 443 (20), 442 [*M*$^+$] (67), 407 (28), 385 (32), 384 (25), 383 (100), 343 (25). $C_{26}H_{35}N_2O_2Cl$ calcd 442.2387, found 442.2375 (MS). calcd: C 70.49, H 7.96, N 6.32; found: C 70.83, H 7.84, N 6.14. $[\alpha]_D^{20}$ = −126.7 (*c* = 0.3, CH_2Cl_2).

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