CHEMISTRY
A EUROPEAN JOURNAL

ChemPubSoc
Europe

DOI: 10.1002/chem.201202413

Total Synthesis of (+)-*trans*-Trikentrin A

Iris R. M. Tébéka,[a] Giovanna B. Longato,[b] Marcus V. Craveiro,[a, c] João E. de Carvalho,[b] Ana L. T. G. Ruiz,[b] and Luiz F. Silva, Jr.*[a]

Abstract: Several syntheses have already been reported for *cis*-trikentrins and herbindoles, which are indole alkaloids unsubstituted at the C2 and C3 positions that bear a *trans*-1,3-dimethylcyclopentyl unit. Herein, we describe the first asymmetric and stereoselective synthesis of the more challenging *trans*-trikentrin A as its naturally occurring isomer. Different approaches were investigated and the strategy of choice was a combination of an enzymatic kinetic resolution and a thallium(III)-mediated ring contraction. The antiproliferative activities of the natural product and related intermediates have been tested against human tumor cell lines, leading to the discovery of new compounds with potent antitumor activity.

Keywords: antitumor activity · kinetic resolution · ring contraction · total synthesis · trikentrin

Introduction

Natural products possess a unique ability to act as bioactive agents against a variety of targets due to their potentially relevant, biosynthetically molded structures.[1] Among them, marine natural products display versatile structural features that are seldom encountered in compounds from terrestrial sources.[2] Accordingly, the success rate of clinically useful discovered drugs among tested marine natural products (1 drug per 3140 tested compounds) is higher than the industry average (1 in 5000–10000).[3] Natural products incorporating indole rings, which are often found in compounds from the marine environment, have inspired the development of several important synthetic methods and useful drugs.[4] Usually, indoles are substituted at their very reactive 2- and 3-positions.[4a] However, a few alkaloids lack substituents at these positions. The most important ones are probably trikentrins and herbindoles,[5] which have been isolated from sponges.[6] In addition, a substituted five-membered ring incorporating two stereocenters is fused to the indole moiety (Figure 1). These cyclopenta[*g*]indoles show antimicrobial activity,[6a] cytotoxicity against KB cells,[6b] and are fish antifeedants.[6b] Related compounds can inhibit the human nonpancreatic secretory phospholipase A_2.[7]

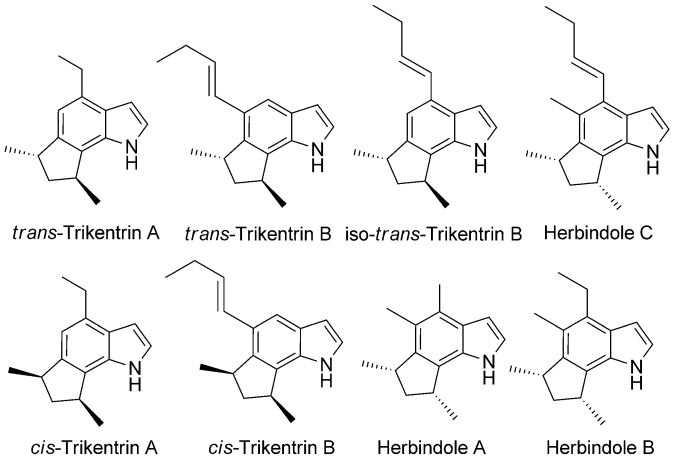


Figure 1. Structures of trikentrins and herbindoles.

Due to their challenging structural features and promising biological activities, an increasing interest in the chemical synthesis of trikentrins and herbindoles has been apparent in recent years.[5,8,9] There have been several total syntheses of the alkaloids containing a *cis*-1,3-dimethylcyclopentyl unit.[5] Asymmetric syntheses of all *cis*-trikentrins and herbindoles have recently been accomplished.[8a,b] However, to the best of our knowledge, there is as yet no stereoselective synthesis for the more challenging *trans*-trikentrins.[9] The reported synthesis of (−)-*trans*-trikentrin A is stereorandom because the target molecule was obtained together with (−)-*cis*-trikentrin A.[8m] The previous racemic syntheses of *trans*-trikentrin A also have serious problems associated with the formation of the *trans*-1,3-dimethylcyclopentyl unit,

[a] I. R. M. Tébéka, Dr. M. V. Craveiro, Prof. L. F. Silva, Jr.
Instituto de Química, Universidade de São Paulo
CP 26077 CEP 05513-970 São Paulo-SP (Brazil)
Fax: (+55 11) 3815-5579
E-mail: luizfsjr@iq.usp.br

[b] G. B. Longato, Prof. J. E. de Carvalho, Dr. A. L. T. G. Ruiz
Centro Pluridisciplinar de Pesquisas Químicas
Biológicas e Agrícolas, Universidade Estadual de Campinas
Campinas-SP (Brazil)

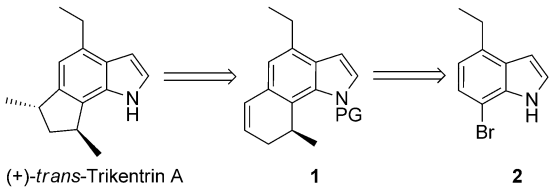
[c] Dr. M. V. Craveiro
Present address: Universidade Federal de São Paulo
R. Prof. Artur Riedel
275 CEP 09972-270 Diadema-SP (Brazil)

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/chem.201202413.

and the best ratio was *cis*/*trans* = 1:1.[8l] In other syntheses, the *trans* isomer was the minor component (4:3[8m] and 55:40[8k]). We developed a protocol for the synthesis of *trans*-1,3-disubstituted indanes through thallium(III)[10a,e]- or iodine(III)[10b,c]-mediated ring contraction[10e–g] of 1,2-dihydronaphthalenes. This reaction was applied in the synthesis of (±)-*trans*-trikentrin A[9a] and of other small molecules.[10c,d,h] In this context, we describe herein the first asymmetric synthesis of (+)-*trans*-trikentrin A, using an enzymatic resolution and a ring-contraction reaction as key steps. The chemical synthesis of small-molecule natural products has an important role in the discovery of new anticancer candidates.[11] Considering the potential biological activity of indole compounds,[12] the antiproliferative activities of the target molecule and analogues have been investigated, leading to the discovery of some potent antitumor compounds.

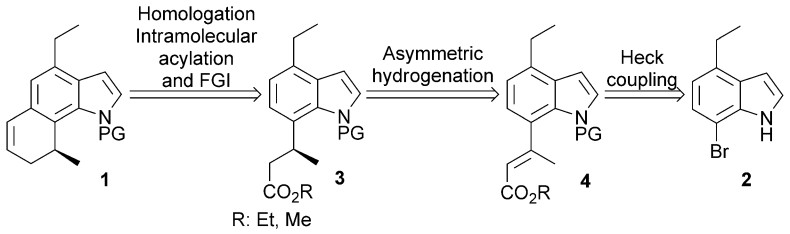
Results and Discussion

Our retrosynthesis of (+)-*trans*-trikentrin A was centered on the use of a ring contraction of the cyclohexene derivative **1** (Scheme 1). This transformation is probably the most efficient method for constructing the required *trans*-1,3-disubstituted indane ring.[10,13] From the outset, we envisaged that the tricyclic intermediate **1** could be prepared in an optically active fashion from bromoindole **2** by several routes. In practice, we had to struggle through different alternatives to finally achieve this goal.



Scheme 1. Ring-contraction approach for (+)-*trans*-trikentrin A. PG = protecting group.

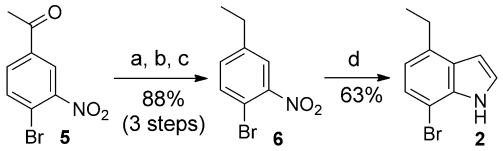
The first approach toward the synthesis of **1** was through an asymmetric hydrogenation of **4** that would lead to alkene **1** after homologation, intramolecular acylation, and the interconversion of functional groups. Alkene **4** would be obtained from bromoindole **2** by a Heck coupling (Scheme 2).



Scheme 2. First retrosynthetic approach to access cyclic alkene **1**. FGI = functional group interconversion.

This strategy was based on our racemic synthesis of *trans*-trikentrin A.

Our first target was the preparation of **2**, which was obtained in four steps from **5**, by using the Bartoli reaction to construct the indole ring (Scheme 3).[14] The preparation of



Scheme 3. Preparation of bromoindole **2**. a) $NaBH_4$, MeOH; b) Ph_3P, I_2, imidazole, CH_2Cl_2; c) $NaBH_4$, DMSO; d) CH_2=CHMgBr, THF.

6 was described in one step from 1-bromo-4-ethylbenzene by nitration, which gave a mixture of two products from which **6** could be obtained in 35% yield after separation of the isomers.[8a] Nevertheless, in three steps and within a few hours, compound **6** was obtained in 88% overall yield on a 10 g scale.

The asymmetric reduction of α,β-unsaturated esters can be performed by using cobalt semicorrins as catalysts and $NaBH_4$ as the reducing agent.[15a,b] Pfaltz and co-workers have also developed various iridium catalysts to perform the asymmetric hydrogenation of nonfunctionalized alkenes.[15c–e] Several iridium catalysts[15f–j] and a cobalt-complexed semicorrin were tested under different conditions for the asymmetric reduction of **12** (Figure 2 and Table 1),

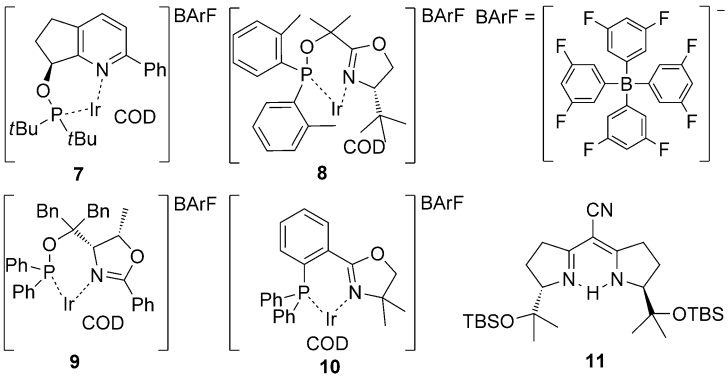


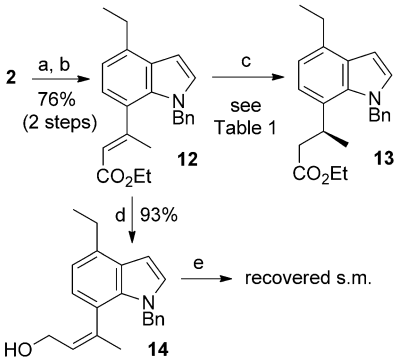
Figure 2. Catalysts for asymmetric hydrogenation. COD = 1,5-cyclooctadiene.

which was obtained from indole **2** by protection with benzyl bromide followed by a Heck reaction (Scheme 4). However, low conversions and *ee* values were usually observed. The best result was obtained by using the catalyst **9**, which gave the desired product **13** with 57% *ee*

Table 1. Conditions for asymmetric reduction of **12**.

Entry	Cat. [mol%]	*P* [bar]	*T* [°C]	*t* [h]	Solvent	Product (Conversion [%]; *ee* [%])[a]
1	Pd/C (10)	100	RT	2	THF	Recovered s.m.
2	$Pd(OH)_2$/C (10)	30	RT	14	THF	Recovered s.m./**13** (2:1; –)
3	**7** (1)	50	RT	2	CH_2Cl_2	Recovered s.m.
4	**7** (1)	50	40	16	CH_2Cl_2	(*S*)-**13** (10; n.d.)
5	**7** (5)	50	40	14	CH_2Cl_2	(*S*)-**13** (10; 36)
6	**7** (1)	70	55	62	CH_2Cl_2	(*S*)-**13** (10; 24)
7	**8** (1)	50	RT	2	CH_2Cl_2	Recovered s.m.
8	**8** (1)	50	40	16	CH_2Cl_2	(*S*)-**13** (9; n.d.)
9	**8** (5)	50	40	14	CH_2Cl_2	(*S*)-**13** (15; 6)
10	**8** (1)	70	55	62	CH_2Cl_2	(*S*)-**13** (10; 24)
11	**9** (1)	50	RT	2	CH_2Cl_2	Recovered s.m.
12	**9** (1)	50	40	16	CH_2Cl_2	(*S*)-**13** (16; n.d.)
13	**9** (5)	50	40	14	CH_2Cl_2	(*S*)-**13** (23; 57)
14	**9** (1)	70	55	62	CH_2Cl_2	(*S*)-**13** (15; 30)
15	**10** (1)	50	RT	2	CH_2Cl_2	Recovered s.m.
16	**10** (2)	50	40	16	CH_2Cl_2	(*S*)-**13** (9; –)
17	**10** (2)	70	55	62	CH_2Cl_2	**13** (9; –)
18	**11** (10)[b]	atmospheric	RT	48	EtOH/DMF	Recovered s.m.

[a] Suggested absolute configuration based on the literature.[15] [b] Complexed with $CoCl_2$. $NaBH_4$ (2 equiv) was used as reducing agent.



Scheme 4. First approach: asymmetric hydrogenation . a) KOH, BnBr, DMSO; b) ethyl crotonate, $PdCl_2$, P(*o*-tol)$_3$, Et_3N, MeCN; c) asymmetric hydrogenation; d) DIBAL, toluene; e) catalyst **7**, **8**, **9**, or **10**, H_2 (50 bar). Bn = benzyl; s.m. = starting material; *o*-tol = *ortho*-tolyl; DIBAL = diisobutylaluminum hydride.

at 23% conversion (Table 1, entry 13). We also attempted without success the hydrogenation of compounds related to **12**, such as the alcohol **14**. Steric hindrance due to the benzyl group may have prevented the catalyst–H_2 complex from reaching the double bond of the substrate. Additionally, the low reactivities of **12** and **14** may have been due to catalyst poisoning by the indole moiety.

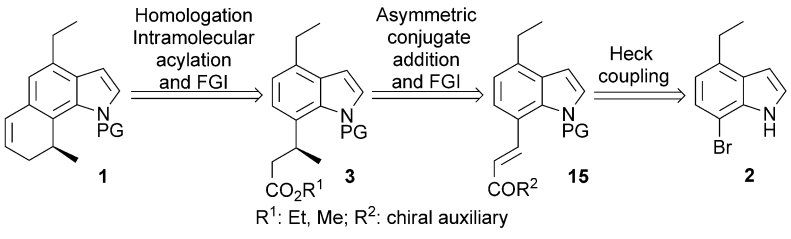
Our second approach was related to an asymmetric conjugate addition to obtain **3** from **15**. A chiral auxiliary would be used in the conjugate addition, and a Heck coupling between bromoindole **2** and an appropriate olefin would form **15** (Scheme 5).

Among the available methods for this transformation, the most suitable to obtain **19** appeared to be that described by Dambacher et al.[16] The required intermediate **18** was prepared by a convergent strategy that involved Heck coupling of **2** and the chiral olefin **17**[17] followed by protection. Alkene **17** was obtained from commercially available pyrrolidinone **16** and freshly prepared acryloyl chloride.[18] Unfortunately, the desired product **19** was not detected in any reaction (Scheme 6).

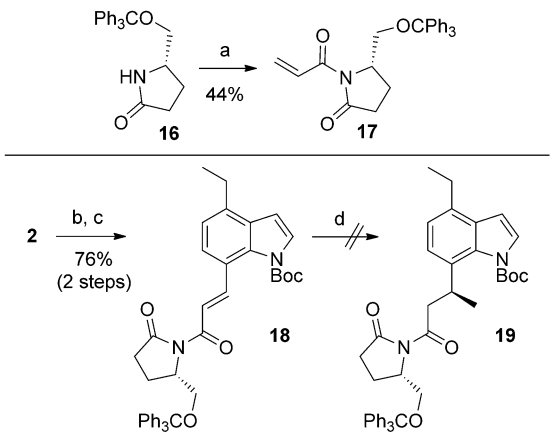
Our third approach involved an aryl coupling to an iron complex.[19a] Intermediate **1** would be accessed after functional group interconversion and intramolecular acylation of **20**. An aryl coupling of indoline **21** with an iron complex[20] obtained from a lactic acid derivative would form ester **20** in a convergent manner (Scheme 7).

Indoline **27** was prepared from **2** in three nonoptimized steps. Treatment of **27** with *s*BuLi led to metallation of the indole, as confirmed by interception with DMF (see the Supporting Information for details). Complex **26** was obtained from the lactic acid derivative **22** by an adapted route.[19b] Oxidation of alcohol **23** to aldehyde **24** could also be achieved with SIBX (stabilized 2-iodoxybenzoic acid),[21] but in lower yield (57%) and after a delicate purification. The coupling of cuprate **29** and the iron complex **26** did not take place under any of the investigated conditions (Scheme 8).[19c] These three approaches taught us that powerful reactions for benzenic systems became inefficient for the corresponding substrates with indole-type rings.

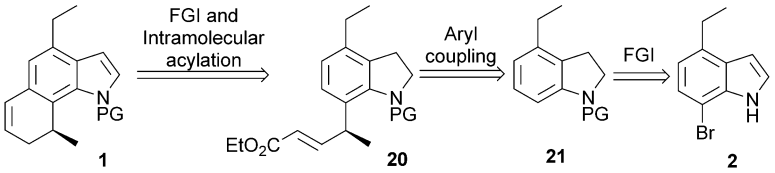
Biocatalysis has recently been used in various total syntheses of natural products.[22a,b] The mild conditions usually required for enzymatic resolution, coupled with the high selectivity and substrate specificity of enzymes,[22b,c] make it a powerful tool in organic synthesis[22b] and in industry.[22d]



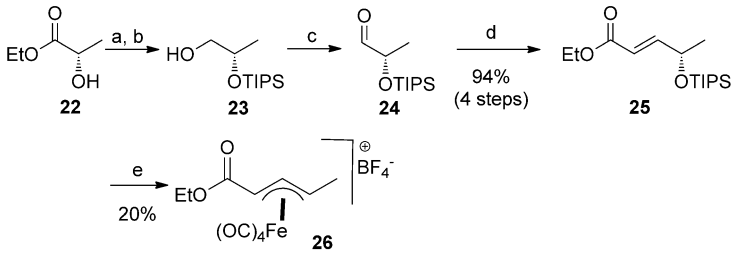
Scheme 5. Second retrosynthetic approach toward cyclic alkene **1**.

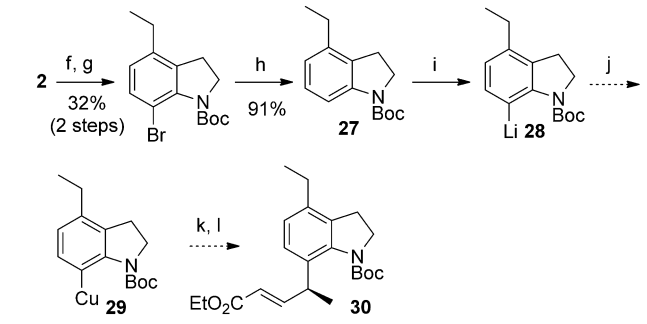


Scheme 6. Second approach: asymmetric conjugate addition. a) 1) *n*BuLi, 2) acryloyl chloride; b) **17**, $Pd(OAc)_2$, P(*o*-tol)$_3$, Et_3N, DMF; c) Boc_2O, DMAP, CH_2Cl_2; d) CuI, MeLi. Boc = *tert*-butoxycarbonyl; DMAP = 4-dimethylaminopyridine.



Scheme 7. Third retrosynthetic approach to obtain alkene **1**.



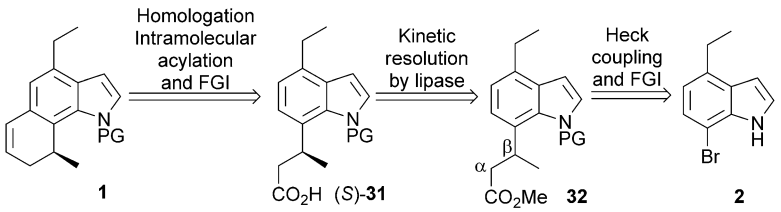


Scheme 8. Third approach: aryl coupling. a) TIPSCl, imidazole, DMF; b) $LiBH_4$, MeOH, Et_2O; c) IBX, EtOAc; d) ethyl phosphonoacetate, NaH, THF; e) $[Fe_2(CO)_9]$, Et_2O; f) $NaCNBH_4$, AcOH; g) Boc_2O, DMAP, CH_2Cl_2; h) 1) *n*BuLi, THF, 2) H_3O^+; i) *s*BuLi, TMEDA, Et_2O; j) CuBr·SMe_2; k) **26**; l) CAN. TIPS = triisopropylsilyl; IBX = 2-iodoxybenzoic acid; TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine; CAN = ceric ammonium nitrate.

Our fourth and successful approach toward the synthesis of (+)-*trans*-trikentrin A was based on lipase-mediated kinetic resolution of ester **32**, obtained from **2** (Scheme 9).

The stereocenter of ester **34** is not on the α-, but on the β carbon atom, that is, more distant from the reactive center (Scheme 10). This not only makes the kinetic resolution more challenging, but also reduces the chances of finding suitable methods to racemize the nonreactive enantiomer. We performed an enzyme screening to find the optimal conditions, and ester **34** was the substrate of choice as its synthesis has been reported previously,[9a] thus avoiding the need for optimization. The (*S*)-selective lipase-mediated hydrolysis of related substrates has been reported to proceed with high *ee* by using *Pseudomonas cepacia* lipase (PCL).[23] Such (*S*)-selectivity of PCL has also been reported for the hydrolysis of β-amino esters.[24] We assumed at this point that the acid obtained from the kinetic resolution by the screened lipases would be the (*S*)-enantiomer. The (*S*)-enantioselectivity would only be confirmed at the end of the synthesis, by comparing the optical rotation of the target molecule with that of the natural product. After much experimentation (Table 2), we found that (*S*)-**35** could be obtained with 99% *ee* in 38% yield by using the enzyme Amano PS-CII (Table 2, entry 6), which is a formulation of PCL immobilized on a ceramic substrate. Shorter (Table 2, entry 5) or longer (Table 2, entry 7) reaction times were found to decrease the yield, and decomposition products were formed after a 109 h cycle. However, when scaling up we found that the production of this enzyme has been discontinued. In a second screening, PS-IM (PCL immobilized on diatomaceous earth) gave (*S*)-**35** with 99% *ee* in 32% isolated yield (Table 2, entry 10). It is known that the amount of water in the reaction mixture determines the direction of lipase-catalyzed reactions.[25a] As hydrolysis is favored over transesterification in the presence of water, the water content in the reaction mixture was increased (Table 2, entries 11–13). However, even after longer reaction times (Table 2, entry 12), lower yields were obtained. Compound (*S*)-**35** has the potential to be used in the total synthesis of (+)-*cis*-trikentrin A.[8a]

Considering that a Boc group would be better than Bn in the ring contraction,[26] we investigated the preparation of (*S*)-**39**. Unfortunately, neither the reduction of **36** nor the resolution of **38** gave the desired product in a practicable manner (Scheme 11). It is known that, as is the case for the majority of enzymes, the enantioselectivity of PCL is highly substrate-dependent, and small structural modifications can significantly alter the *ee*.[25] Substrate recognition is driven by diastereoselective nonbonding interactions formed by the substrate at the active site of the enzyme, where aromatic rings are optimally accommodated. Also, hydrolysis can be prevented by steric hindrance in the vicinity of the active



Scheme 9. Fourth and successful retrosynthetic approach to access alkene **1**.

Table 2. Enzyme screening for kinetic resolution[a] of ester **34**.

Entry	Enzyme	Solvent	Yield of (*S*)-**35** [%]	*ee* [%]
1	PS-D	Et_2O	19[b]	97
2	PS-D	DIPE	8[b]	99
3	PS-CII	Et_2O	26	95
4	PS-CII	DIPE	34	99
5	PS-CII	DIPE	27[c,d]	99
6	PS-CII	DIPE	38[c]	99
7	PS-CII	DIPE	12[c,e]	99
8	PS-IM	Et_2O	4[b]	99
9	PS-IM	DIPE	21[b]	99
10	PS-IM	DIPE	32[c]	99
11	PS-IM	DIPE	15[f]	99
12	PS-IM	DIPE	23[c,f]	99
13	PS-IM	DIPE	7[g]	99
14	PS-IM	DIPE	21[h]	99
15	CALB	Et_2O	n.d.	–
16	CALB	DIPE	1	0
17	CALB	phosphate buffer[i]	n.d.	–
18	PPL	Et_2O	1	0
19	PPL	DIPE	1	0
20	PPL	phosphate buffer[i]	n.d.	–
21	Novozym 435	DIPE	n.d.	–
22	*Pseudomonas cepacia* (free)	Et_2O	1	0
23	*Pseudomonas cepacia* (free)	DIPE	1	0
24	*Pseudomonas sp.* in cellulose	Et_2O	n.d.	–
25	*Pseudomonas sp.* in cellulose	DIPE	1	0
26	*Penicillium camembertii*	Et_2O	1	27
27	*Penicillium camembertii*	DIPE	1	3
28	*Mucor meihei*	Et_2O	n.d.	–
29	*Mucor meihei*	DIPE	1	0
30	*Aspergillus niger*	Et_2O	1	4
31	*Aspergillus niger*	DIPE	1	0
32	*Pseudomonas fluorescens*	Et_2O	21	91
33	*Pseudomonas fluorescens*	DIPE	1	0
34	*Mucor javanicus*	Et_2O	2	97
35	*Mucor javanicus*	DIPE	1	3
36	*Candida cylindracea*	Et_2O	n.d.	–
37	*Candida cylindracea*	DIPE	1	0
38	*Candida rugosa*	Et_2O	1	6
39	*Candida rugosa*	DIPE	1	0

[a] 1 mg enzyme per 1 mg substrate, 0.5 mol L^{-1}, H_2O (4 equiv), 65 h. [b] Isolated yields. Other yields were calculated by HPLC. [c] After 2 cycles on a 0.3 mmol scale. [d] 43 h cycle. [e] 109 h cycle, decomposition products observed. [f] 10 equivalents of H_2O were used. [g] 20 equivalents of H_2O were used. [h] 95 h cycle. [i] 1 mg enzyme per 1 mg of substrate, 1 mol L^{-1} phosphate buffer, pH 7, MeOH, 40 °C, 65 h.

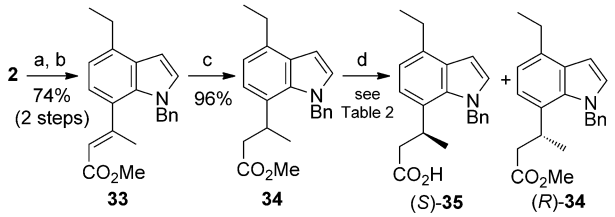
site.[27] The reason why the kinetic resolution of ester **38** was not observed to any extent may be the replacement of the benzyl group by Boc, as one less aromatic ring was available to facilitate the substrate accommodation inside the active site of the enzyme.

Having established a reliable procedure to obtain (*S*)-**35**, we worked toward its homologation. After achieving good results with a model substrate by using the Kowalski homologation,[28] the relevant conditions were applied to (±)-**34**. The required dibromoketone **40** was prepared in good yield. However, the next step did not proceed under any of the conditions tested (Scheme 12). As an excess of *n*BuLi was needed, reactive positions C2 and C3 may have been metallated, leading to several unidentified products.

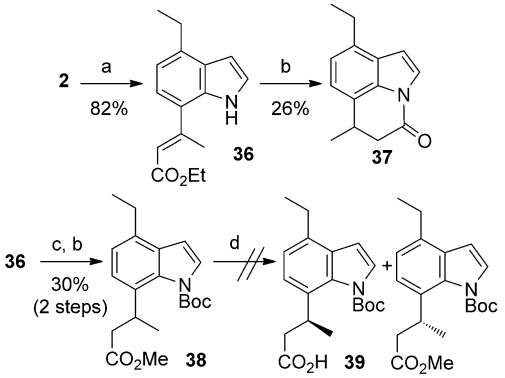
The desired homologated acid (*S*)-**42** was obtained in 73% overall yield by a robust four-step sequence from (*S*)-**35**. Acid (*S*)-**42** was cyclized to yield (*S*)-**43** and the protecting group was changed to the electron-withdrawing Boc[29] to afford (*S*)-**45**, which was reduced and dehydrated to yield (*S*)-**46** (Scheme 13).

The cyclic alkene (*S*)-**46** was treated with thallium trinitrate trihydrate (TTN) and $NaBH_4$ to promote the ring contraction. The aldehyde formed in situ was reduced to alcohol **47** to avoid any epimerization. Remarkably, electrophilic Tl^{III} was found to react with the alkene without disturbing the highly reactive indole ring.[26] Additionally, only the *trans* diastereomer was formed during this rearrangement. The alcohol moiety of **47** was then reduced to the corresponding alkane, delivering (+)-*trans*-trikentrin A ($[\alpha]_D^{25} = +24°$, $c = 0.00125$ in $CHCl_3$; Scheme 14). The optical rotation of the target molecule was equivalent to the reported value for the natural product,[6a] thus confirming the (*S*)-selectivity of PCL towards ester **34** during the kinetic resolution and indicating that there was no epimerization in any reaction after the resolution.

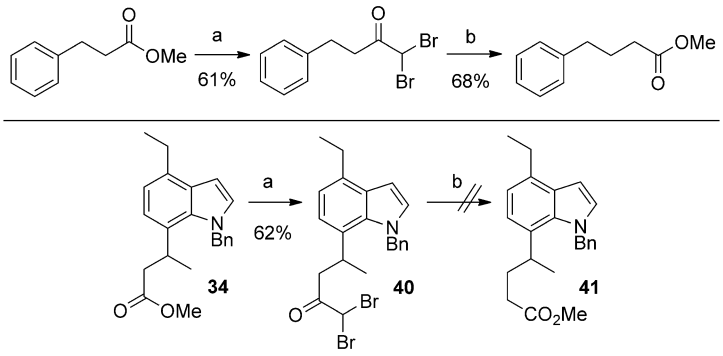
The tosylate reduction and Boc deprotection of **48** were not expected to be accomplished in a single step, because Boc groups are usually stable in the presence of $NaBH_4$.[30] *N*-Boc-amines have also been reported to be deprotected in the presence of water at 100 °C, acting as an acid–base catalyst.[31] Moreover, the neat thermolysis of Boc groups has been reported, with the temperature varying according to the substrate structure.[8b,32] We believe that when heating **48**, the water present in DMSO might have favored the deprotection. The presence of $NaBH_4$ coupled with a long heating time may also have played a role in producing the observed results. A qualitative experiment was set up to identify the determining factor in the Boc deprotection of **48**. *N*-Boc indole **49** was heated in parallel reactions that were followed by TLC (Scheme 15). Reactions a) and c) led exclusively to the deprotected indole **50**, but heating **49** in anhydrous



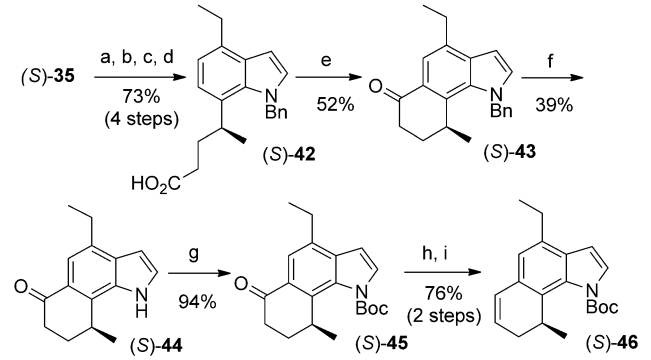
Scheme 10. Fourth and successful approach: kinetic resolution of **34** by lipase. a) KOH, BnBr, DMSO; b) methyl crotonate, $PdCl_2$, P(*o*-tol)$_3$, Et_3N, MeCN; c) Mg, MeOH; d) kinetic resolution.



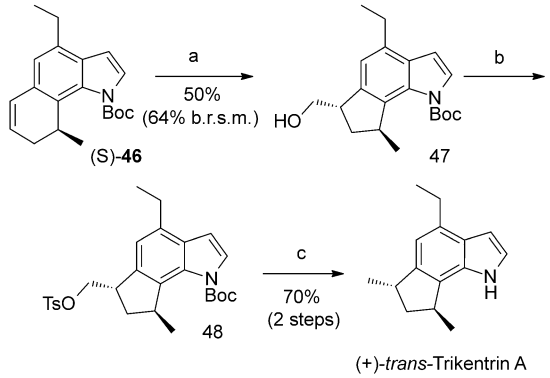
Scheme 11. Tentative preparation of (*S*)-**39**. a) Ethyl crotonate, $PdCl_2$, P(*o*-tol)$_3$, Et_3N, MeCN; b) Mg, MeOH; c) Boc_2O, DMAP, CH_2Cl_2; d) PS-CII, DIPE, H_2O. DIPE = diisopropyl ether.



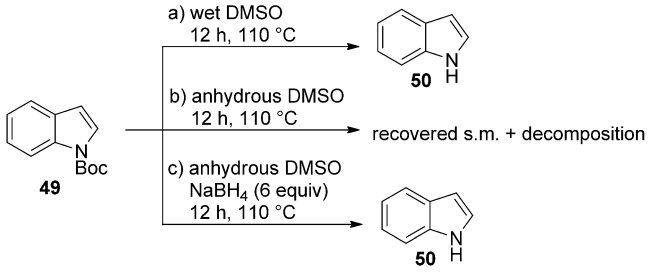
Scheme 12. Kowalski homologation of a model compound and tentative preparation of **41**. a) TMP, *n*BuLi, CH_2Br_2, THF; b) 1) HMDS, *n*BuLi, 2) *n*BuLi, 3) MeOH/HCl. TMP = 2,2,6,6-tetramethylpiperidine; HMDS = hexamethyldisilazane.



Scheme 13. Preparation of tricyclic indole (*S*)-**46**. a) BH_3·SMe_2, MeOH, Et_2O; b) MsCl, DMAP, pyridine, CH_2Cl_2; c) KCN, DMSO; d) KOH, ethylene glycol, H_2O; e) TFA, TFAA; f) $AlCl_3$, anisole; g) Boc_2O, DMAP, CH_2Cl_2; h) $NaBH_4$, MeOH; i) H_3PO_4, DMF. Ms = mesyl; TFA = trifluoroacetic acid; TFAA = trifluoroacetic anhydride.



Scheme 14. Final steps toward (+)-*trans*-trikentrin A. a) 1) TTN, MeCN, 2) $NaBH_4$; b) TsCl, Et_3N, pyridine, CH_2Cl_2; c) $NaBH_4$, DMSO. TTN = thallium(III) nitrate trihydrate; Ts = tosyl; b.r.s.m. = based on recovered starting material.



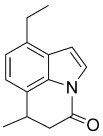
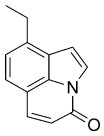
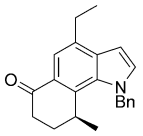
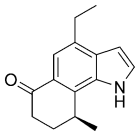
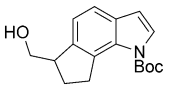
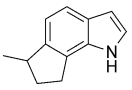
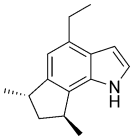
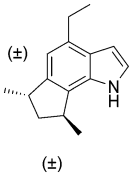
Scheme 15. Tested conditions for the deprotection of **49**.

DMSO without $NaBH_4$ did not form **50** and a decomposition product was observed. Thus, either water or $NaBH_4$ is capable of deprotecting indole substrates upon heating in DMSO.

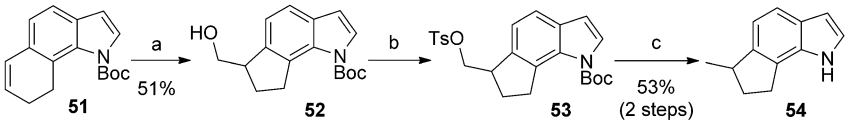
The indole **54** was synthesized from alkene **51**[26] to broaden the variety of analogues to be tested against human tumor cell lines (Scheme 16).

The in vitro antiproliferative activities of the target molecule and related compounds were evaluated toward human tumor cell lines (Table 3). According to the mean log GI_{50} values,[33] the tested compounds showed moderate cytostatic effects, except for **52**, which showed only weak activity, and **55**, which appeared to be inactive. The moderately active compounds displayed different selectivity profiles. The extended conjugation present in **55** would seem to dramatically impair its activity, as the structurally related compound **37** showed moderate activity. Compounds (*S*)-**43** and (*S*)-**44**, which differ only in the protecting group, showed moderate

Table 3. Antiproliferative activities (GI_{50}, $\mu g\,mL^{-1}$) of (+)-*trans*-trikentrin A and its analogues.[a]

Entry	Doxo-rubicin	 **37**	 **55**	 (*S*)-**43**	 (*S*)-**44**	 **52**[b]	 **54**	 (+)-*trans*-trikentrin A	 (±)-*trans*-trikentrin A
U251	0.106	3.1	>250	3.0	18.9	25.6	4.4	19.7	N.T.
MCF-7	0.062	4.3	>250	6.9	21.4	26.3	18.1	2.8	29.0
NCI-ADR/RES	3.842	5.6	>250	2.6	**0.42**	31.5	**0.36**	2.5	9.2
OVCAR-3	0.336	7.4	>250	3.1	17.2	25.5	17.4	3.1	2.8
786-0	0.139	4.0	>250	10.6	20.8	28.5	19.0	12.2	22.1
NCI-H460	0.080	7.4	>250	8.1	10.5	41.4	18.2	21.7	2.8
PC-3	0.146	10.2	>250	6.1	7.6	40.4	9.8	6.6	22.6
UACC-62	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	3.7
HT-29	N.T.	N.T.	N.T.	N.T.	N.T.	N.T.	8.9	N.T.	9.6
HaCat	0.115	5.3	>250	4.7	8.1	22.1	4.2	4.5	N.T.
Mean LogGI$_{50}$	−0.350	0.74	>2.40	0.70	0.95	1.47	0.86	0.82	1.07

[a] U251: glioma; MCF-7: breast; NCI-ADR/RES: ovarian resistant to multiple drugs; OVCAR-3: ovarian; 786-0: kidney; NCI-H460: lung, nonsmall cells; PC-3: prostate; UACC-62: melanoma; HT-29: colon; VERO: green monkey epithelial kidney cell; HaCat: human keratinocyte, immortalized normal cell; N.T.: not tested.



Scheme 16. Concomitant reduction and deprotection toward **54**. a) 1) TTN, MeCN, 2) $NaBH_4$; b) TsCl, Et_3N, CH_2Cl_2; c) $NaBH_4$, DMSO.

activity. However, (*S*)-**44** inhibited the growth of adryamycin-resistant ovarian tumor cells (NCI-ADR/RES) more potently ($GI_{50}=0.42\,\mu g\,mL^{-1}$) than that of other cell lines (GI_{50} from 7.6 to 21.4 $\mu g\,mL^{-1}$). A similar profile was observed for indole **54** ($GI_{50}=0.36\,\mu g\,mL^{-1}$ for NCI-ADR/RES; other cell lines: GI_{50} from 4.2 to 19.0 $\mu g\,mL^{-1}$). It is important to note that compound **54** can be prepared in only seven steps from 1-tetralone. (+)-*trans*-Trikentin A proved to be slightly more active (mean $\log GI_{50}=0.82$) than (±)-*trans*-trikentin A (mean $\log GI_{50}=1.07$).

Conclusion

The first total synthesis of (+)-*trans*-trikentrin A has been achieved by using a kinetic resolution performed by a lipase and a thallium(III)-mediated ring contraction as key steps. The antiproliferative activities of several molecules have been tested, and the results pointed to (*S*)-**44** and **54** as promising lead compounds against drug-resistant ovarian cell lines. The synthesis of (+)-*cis*-trikentrin A can be envisaged from (*S*)-acid **35**. A short synthesis of this natural product and the cytotoxic activities of related intermediates are under evaluation.

Experimental Section

7-Bromo-4-ethyl-1*H*-indole (2): A Schlenk flask was loaded with **6** (480 mg, 2.11 mmol) under N_2 atmosphere, anhydrous THF (50 mL) was added, and the solution was cooled to −45 °C. A 1 $mol\,L^{-1}$ solution of vinylmagnesium bromide in THF (7.40 mL, 7.40 mmol, 3.5 equiv) was added dropwise. After 45 min under stirring, a saturated aqueous solution of NH_4Cl was slowly added and the mixture was allowed to warm to RT. The aqueous phase was extracted with Et_2O and the organic layer was washed with a saturated aqueous solution of NH_4Cl and with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the remaining crude material was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1) to afford **2**[9a] (300 mg, 1.34 mmol, 63 %) as a brown oil.

1-Bromo-4-ethyl-2-nitrobenzene (6): $NaBH_4$ (2.355 g, 61.97 mmol, 1.5 equiv) was slowly added to a stirred solution of the starting acetophenone **5** (10.080 g, 41.31 mmol) in MeOH (80 mL) at 0 °C, and the mixture was allowed to warm to RT. After stirring for 30 min, H_2O was added and the aqueous layer was extracted with EtOAc. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the remaining crude alcohol was dissolved in CH_2Cl_2 (200 mL). Ph_3P (16.235 g, 61.97 mmol, 1.5 equiv) and imidazole (4.214 g, 61.97 mmol, 1.5 equiv) were then added and the mixture was cooled to 0 °C. Molecular iodine (15.740 g, 61.97 mmol, 1.5 equiv) was added, the cold bath was removed, and after stirring for 3 h, H_2O was added and the mixture was extracted with CH_2Cl_2. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was kept under high vacuum for 1.5 h. The product was then dissolved in DMSO (150 mL) and the solution was cooled to 0 °C. Sodium borohydride (3.140 g, 82.62 mmol, 2 equiv) was slowly added, the reaction mixture was allowed to warm to RT and stirred for 30 min, and then cooled to 0 °C once more. H_2O was added and the aqueous phase was extracted with EtOAc. The organic phase was washed with brine, dried over anhydrous $MgSO_4$, and the solvent was evaporated under reduced pressure to

afford the crude product as a yellow solid. This product was dissolved in the minimum volume of CH_2Cl_2 and then a mixture of hexane/Et_2O (1:1; 100 mL) was added. After gentle shaking, Ph_3PO started to precipitate. The mixture was then filtered through a silica pad with Et_2O, and the pad was washed with Et_2O until no more product was eluted, as monitored by TLC. This procedure removed most of the Ph_3PO formed as a byproduct. The eluent was collected and concentrated under reduced pressure, and the crude product was purified by column chromatography (hexanes/EtOAc, 9:1) to afford compound **6**[9a] (8.393 g, 36.49 mmol, 88% over three steps) as a yellow oil.

1-Acryloyl-5-trityloxymethylpyrrolidin-2-one (17): An N_2-filled Schlenk flask was loaded with **16** (71 mg, 0.20 mmol) and anhydrous THF (5 mL) was added. The solution was cooled to −78 °C, whereupon a 2 mol L^{-1} solution of *n*BuLi in hexanes (0.11 mL, 0.22 mmol, 1.1 equiv) was added dropwise. After stirring for 45 min, acryloyl chloride[18a] (0.02 mL, 0.24 mmol, 1.2 equiv) was added dropwise and the reaction mixture was stirred for 30 min. Saturated aqueous NH_4Cl solution (1 mL) was then added, the mixture was allowed to slowly warm to RT, and then diluted with H_2O. It was extracted with Et_2O, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography (hexanes/EtOAc, 8:2→7:3) to afford **17** (37 mg, 0.09 mmol, 44%) as a light-yellow oil that solidified as a white material upon standing. M.p. 133–135 °C; $[\alpha]_D^{25} = -123.2°$ ($c = 0.005$ g cm^{-3} in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.54$ (dd, $J = 17.1$, 10.5 Hz, 1H), 7.37–7.19 (m, 15H), 6.46 (dd, $J = 17.1$, 2.1 Hz, 1H), 5.86 (dd, $J = 10.5$, 2.1 Hz, 1H), 4.56–4.51 (m, 1H), 3.59 (dd, $J = 9.9$, 2.7 Hz, 1H), 3.16 (dd, $J = 9.9$, 2.7 Hz, 1H), 3.05–2.92 (m, 1H), 2.51 (qd, $J = 9.9$, 2.1 Hz, 1H), 2.19–1.96 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.5$, 165.7, 143.6 (3C), 130.6, 129.6, 128.5 (6C), 127.9 (6C), 127.1 (3C), 87.1, 64.0, 56.8, 33.2, 21.2 ppm; IR (KBr): $\tilde{\nu}_{max} = 3058$, 2930, 1737, 1681, 1231 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $[C_{27}H_{25}NO_3+Na]^+$: 434.1732; found: 434.1735.

(*E*)-*tert*-Butyl 4-ethyl-7-{3-oxo-3-[2-oxo-5-(trityloxymethyl)pyrrolidin-1-yl]prop-1-enyl}-1*H*-indole-1-carboxylate (18): A solution of the starting bromoindole **2** (284 mg, 1.27 mmol) in anhydrous DMF (15 mL) was added to a Schlenk flask under an N_2 atmosphere. The chiral olefin **17** (557 mg, 1.4 mmol, 1.1 equiv), a solution of $Pd(OAc)_2$ (28 mg, 0.127 mmol, 0.1 mmol) in DMF (1 mL), a solution of P(*o*-tolyl)$_3$ (193 mg, 0.64 mmol, 0.5 equiv) in DMF (1 mL), and Et_3N (0.66 mL, 5.08 mmol, 4 equiv) were then added sequentially to the stirred solution. The reaction mixture was heated to 120 °C and stirred for 10 h. It was then cooled to RT and diluted with brine (50 mL). The resulting mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the remaining brown oil was used in the next step without further purification. To this end, it was placed in a Schlenk flask under N_2 atmosphere, anhydrous CH_2Cl_2 (5 mL) was added, followed by DMAP (15 mg, 0.127 mmol, 0.1 equiv) and Boc_2O (415 mg, 1.91 mmol, 1.5 equiv). After stirring for 1 h, H_2O was added and the aqueous layer was extracted with CH_2Cl_2. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexanes/EtOAc, 95:5→9:1→8:2→7:3) to afford **18** (631 mg, 0.965 mmol, 76%) as a yellow oil that solidified under vacuum or upon standing. M.p. 70–72 °C; $[\alpha]_D^{25} = -35.8°$ ($c = 0.00167$ g cm^{-3} in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 8.45$ (d, $J = 15.6$ Hz, 1H), 7.93 (d, $J = 15.6$ Hz, 1H), 7.67 (d, $J = 7.8$ Hz, 1H), 7.61 (d, $J = 3.5$ Hz, 1H), 7.40–7.34 (m, 6H), 7.30–7.17 (m, 9H), 6.66 (d, $J = 3.5$ Hz, 1H), 4.65–4.62 (m, 1H), 3.64 (dd, $J = 9.6$, 3.9 Hz, 1H), 3.20 (dd, $J = 9.6$, 2.4 Hz, 1H), 3.07–2.97 (m, 1H), 2.90 (q, $J = 7.7$ Hz, 2H), 2.53 (ddd, $J = 17.7$, 9.6, 1.8 Hz, 1H), 2.19–1.94 (m, 1H), 1.59 (s, 9H), 1.32 ppm (t, $J = 7.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 176.5$, 166.1, 150.0, 145.6, 143.7 (3C), 139.0, 133.7, 131.1, 128.6 (6C), 128.3, 127.9 (6C), 127.1 (3C), 125.0, 122.2, 121.2, 116.9, 105.5, 87.0, 84.5, 64.3, 56.9, 33.5, 27.9 (3C), 26.0, 21.2, 14.8 ppm; IR (KBr): $\tilde{\nu}_{max} = 2971$, 1744, 1673, 1609, 1491 cm^{-1}; HRMS (ESI): *m*/*z* calcd for $[C_{42}H_{42}N_2O_5+Na]^+$: 677.2991; found: 677.2994.

4-Ethyl-2,3-dihydro-1-*tert*-butoxycarbonyl indole (27): *tert*-Butyl-7-bromo-4-ethylindoline-1-carboxylate (19 mg, 0.058 mmol) was placed in an N_2-filled Schlenk flask and anhydrous THF (0.2 mL) was added. The solution was cooled to −78 °C and a 2.03 mol L^{-1} solution of *n*BuLi in hexanes (0.034 mL, 0.070 mmol, 1.2 equiv) was added dropwise. After stirring for 2 h, the mixture was allowed to warm to RT. Saturated aqueous NH_4Cl solution was then added dropwise and the resulting mixture was extracted with Et_2O. The organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the remaining crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1) to afford **27** (13 mg, 0.053 mmol, 91%) as a light-yellow oil that solidified upon standing. M.p. 39–42 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.69$ (m, 1H), 7.12 (t, $J = 7.8$ Hz, 1H), 6.79 (d, $J = 7.5$ Hz, 1H), 3.98 (t, $J = 8.7$ Hz, 2H), 3.02 (t, $J = 8.7$ Hz, 2H), 2.55 (q, $J = 7.7$ Hz, 2H), 1.56 (s, 9H), 1.20 ppm (t, $J = 7.7$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 152.5$, 142.9, 140.0, 127.5, 124.6, 121.3, 117.2, 112.1, 82.4, 47.4, 28.3 (3C), 25.7, 13.9 ppm; IR (film): $\tilde{\nu}_{max} = 3048$, 2968, 2391, 2873, 1703, 1461, 1398 cm^{-1}; LRMS: *m*/*z* (%): 247 (3) [$M^{+\bullet}$], 191 (27), 146 (30), 130 (11), 117 (18), 57 (100), 41 (50); HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{21}NO_2+H]^+$: 248.1651; found: 248.1622.

(*E*)-Methyl 3-(1-benzyl-4-ethyl-1*H*-indol-7-yl)but-2-enoate (33): The starting bromoindole **2** (249 mg, 1.111 mmol) was placed in a flask and DMSO (5 mL) was added. KOH (249 mg, 4.444 mmol, 4 equiv) was added and the mixture was stirred for 30 min. BnBr (0.16 mL, 1.333 mmol, 1.2 equiv) was added and the resulting mixture was stirred at RT for 12 h. H_2O was used to quench the reaction and then the mixture was extracted with Et_2O. The organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure, the remaining crude product was redissolved in anhydrous MeCN (5 mL), and this solution was transferred to a Schlenk flask previously filled with nitrogen. Methyl crotonate (1.88 mL, 17.776 mmol, 16 equiv), $PdCl_2$ (20 mg, 0.111 mmol, 0.1 equiv), P(*o*-tolyl)$_3$ (68 mg, 0.222 mmol, 0.2 equiv), and anhydrous Et_3N (5 mL) were then added sequentially. The reaction mixture was heated to 110 °C and stirred under a nitrogen atmosphere for 15 h. Brine was then added and the aqueous layer was extracted with EtOAc. The organic phase was washed with H_2O and brine, dried over anhydrous $MgSO_4$, filtered, and concentrated under vacuum. The crude product was purified by flash chromatography (silica gel, 100% hexanes→hexanes/EtOAc, 20:1→10:1→9:1) to afford **33** as a white solid after recrystallization from hexanes containing a drop of CH_2Cl_2. M.p. 68–69 °C; ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.23$–7.20 (m, 3H), 7.09 (d, $J = 3.3$ Hz, 1H), 6.93 (d, $J = 7.5$ Hz, 1H), 6.84–6.80 (m, 3H), 6.65 (d, $J = 3.3$ Hz, 1H), 5.71 (q, $J = 1.3$ Hz, 1H), 5.34 (s, 2H), 3.70 (s, 3H), 2.95 (q, $J = 7.8$ Hz, 2H), 2.28 (d, $J = 1.3$ Hz, 3H), 1.37 ppm (t, $J = 7.8$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.8$, 156.4, 138.2, 136.5, 131.7, 130.1, 129.4, 128.6 (2C), 127.3, 126.3, 126.3 (2C), 121.8, 119.7, 117.7, 100.6, 52.0, 51.0, 26.0, 21.9, 14.5 ppm; IR (film): $\tilde{\nu}_{max} = 2966$, 1717, 1636, 1200, 1162 cm^{-1}; LRMS: *m*/*z* (%): 333 (12) [$M^{+\bullet}$], 260 (17), 244 (8), 196 (10), 167 (19), 91 (100), 65 (27); HRMS (ESI): *m*/*z* calcd for $[C_{22}H_{23}NO_2+H]^+$: 334.1807; found: 334.1820.

Methyl 3-(1-benzyl-4-ethyl-1*H*-indol-7-yl)butanoate (34): Anhydrous MeOH (7.5 mL) and Mg^0 (180 mg, 7.54 mmol, 10 equiv) were added to a flask containing the ester **33** (251 mg, 0.754 mmol). The mixture was slowly heated and after heating at reflux for 13 h it had undergone a color change from light translucent yellow to milky white. After cooling to RT, 10% HCl solution was added until gas evolution stopped. The aqueous layer was extracted with EtOAc and the organic layer was washed with a saturated solution of $NaHCO_3$ and with brine, dried over anhydrous $MgSO_4$, and concentrated under vacuum. The crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1) to furnish **34** (243 mg, 0.725 mmol, 96%) as a light-yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): $\delta = 7.28$–7.17 (m, 3H), 7.09 (d, $J = 7.2$ Hz, 1H), 6.96–6.92 (m, 4H), 6.61 (d, $J = 3.2$ Hz, 1H), 5.76 (d, $J = 17.4$ Hz, 1H), 5.51 (d, $J = 17.4$ Hz, 1H), 3.88–3.76 (m, 1H), 3.57 (s, 3H), 2.95 (q, $J = 7.5$ Hz, 2H), 2.60 (dd, $J = 15.3$, 5.4 Hz, 1H), 2.45 (dd, $J = 15.3$, 9.2 Hz, 1H), 1.36 (t, $J = 7.5$ Hz, 3H), 1.04 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 172.9$, 139.0, 134.4, 132.7, 130.9, 129.7, 128.6 (2C), 127.6, 127.2, 125.7 (2C), 119.5, 118.2, 99.9, 53.1, 51.4, 43.1, 29.6, 25.8, 21.7, 14.4 ppm; IR (film): $\tilde{\nu}_{max} = 2963$, 2930, 2874, 1734, 1501, 1455, 1168 cm^{-1}; LRMS: *m*/*z* (%): 335 (21) [$M^{+\bullet}$], 262 (48), 246 (8), 234 (14), 154 (10), 91

(100), 65 (26); HRMS (ESI): *m/z* calcd for $[C_{22}H_{25}NO_2+H]^+$: 336.1964; found: 336.1958.

(*S*)-3-(1-Benzyl-4-ethyl-1*H*-indol-7-yl)butanoic acid ((*S*)-35): The lipase Amano PS-IM (220 mg) and H_2O (0.047 mL, 2.628 mmol, 4 equiv) were added to a stirred solution of the starting ester **34** (220 mg, 0.657 mmol) in diisopropyl ether (DIPE, 13 mL). The mixture was heated to 40 °C and stirred for 65 h. Anhydrous $MgSO_4$ was then added, and the resulting mixture was filtered to remove the drying agent and the enzyme from the organic layer. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography (hexanes/EtOAc, 9:1→8:2→7:3) to afford the compound (*S*)-**35** (44 mg, 0.138 mmol, 21%, *ee* = 99%) and the remaining starting ester (153 mg, 0.456 mmol, 70%), both as yellow oils. The recovered ester was redeployed in one more cycle, affording after the second cycle the acid (*S*)-**35** in 32% yield with 99% *ee* and the recovered ester in 52% yield with 41% *ee*. $[\alpha]_D^{25} = -14.1°$ ($c = 0.005\ g\,cm^{-3}$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.22–7.17$ (m, 3H), 7.10 (d, $J = 3.3$ Hz, 1H), 6.98–6.92 (m, 4H), 6.62 (d, $J = 3.3$ Hz, 1H), 5.72 (d, $J = 17.4$ Hz, 1H), 5.52 (d, $J = 17.4$ Hz, 1H), 3.88–3.76 (m, 1H), 2.93 (q, $J = 7.8$ Hz, 2H), 2.65 (dd, $J = 15.5$, 5.4 Hz, 1H), 2.48 (dd, $J = 15.9$, 9.0 Hz, 1H), 1.36 (t, $J = 7.8$ Hz, 3H), 1.08 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 178.5$, 138.9, 134.5, 132.7, 131.0, 129.8, 128.7 (2C), 127.4, 127.3, 125.7 (2C), 119.5, 118.3, 100.0, 53.2, 42.9, 29.5, 25.8, 21.9, 14.4 ppm; IR (film): $\tilde{\nu}_{max} = 3028$, 2964, 2928, 2872, 1706, 1501, 1454 cm^{-1}; LRMS: *m/z* (%): 321 (20) [$M^{+\bullet}$], 307 (2), 262 (38), 246 (5), 234 (7), 170 (5), 154 (11), 91 (100); HRMS (ESI): *m/z* calcd for $[C_{21}H_{23}NO_2+H]^+$: 322.1807; found: 322.1815.

(*E*)-Ethyl 3-(4-ethyl-1*H*-indol-7-yl)but-2-enoate (36): Bromoindole **2** (66 mg, 0.295 mmol) was placed in a Schlenk flask under N_2 atmosphere and anhydrous MeCN (1.2 mL) was added, followed by ethyl crotonate (0.58 mL, 4.72 mmol, 16 equiv), $PdCl_2$ (5 mg, 0.029 mmol, 0.1 equiv), P(*o*-tolyl)$_3$ (18 mg, 0.059 mmol, 0.2 equiv), and Et_3N (0.06 mL). The mixture was heated to 110 °C and stirred for 14 h. Brine (2 mL) was then added, the aqueous layer was extracted with EtOAc, and the organic phase was washed with H_2O and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1) to afford **36** (52 mg, 0.202 mmol, 82%) as a brown oil. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.49$ (br s, 1H), 7.24 (d, $J = 3.0$ Hz, 1H), 7.15 (d, $J = 7.5$ Hz, 1H), 6.98 (d, $J = 7.5$ Hz, 1H), 6.63 (dd, $J = 3.3$, 2.1 Hz, 1H), 6.23 (d, $J = 1.5$ Hz, 1H), 4.24 (q, $J = 7.2$ Hz, 2H), 2.94 (q, $J = 7.5$ Hz, 2H), 2.67 (d, $J = 1.5$ Hz, 3H), 1.36 (t, $J = 7.4$ Hz, 3H), 1.33 ppm (t, $J = 7.2$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 166.9$, 155.2, 137.6, 132.4, 127.6, 124.5, 123.9, 121.1, 118.3, 117.4, 59.9, 26.3, 19.7, 14.6, 14.4 ppm; IR (film): $\tilde{\nu}_{max} = 3371$, 2965, 2932, 1621 cm^{-1}; LRMS: *m/z* (%): 257 (26) [$M^{+\bullet}$], 240 (3), 212 (100), 196 (52), 184 (7), 167 (20), 154 (15); HRMS (ESI): *m/z* calcd for $[C_{16}H_{19}NO_2+Na]^+$: 280.1313; found: 280.1314.

9-Ethyl-6-methyl-5,6-dihydro-4*H*-pyrrolo[3,2,1-*ij*]quinolin-4-one (37): Anhydrous methanol (7 mL) was added to a flask previously loaded with **36** (104 mg, 0.405 mmol), followed by Mg^0 (97 mg, 4.05 mmol, 10 equiv). The reaction mixture was heated at reflux for 5 h, whereupon it had become milky white in appearance. It was then cooled to RT, 10% HCl solution was added until acidic pH, and the aqueous layer was extracted with EtOAc. The organic phase was washed with H_2O and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1→8:2) to afford **37** (24 mg, 0.104 mmol, 26%) as a light-yellow oil. ^1H NMR (500 MHz, $CDCl_3$): $\delta = 7.66$ (d, $J = 3.5$ Hz, 1H), 7.10 (dd, $J = 7.5$, 0.5 Hz, 1H), 7.05 (d, $J = 7.5$ Hz, 1H), 6.74 (d, $J = 3.5$ Hz, 1H), 3.46–3.32 (m, 1H), 3.02 (dd, $J = 17.0$, 6.3 Hz, 1H), 2.87 (q, $J = 7.7$ Hz, 2H), 2.72 (dd, $J = 17.0$, 8.5 Hz, 1H), 1.43 (d, $J = 7.0$ Hz, 3H), 1.33 ppm (t, $J = 7.7$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta = 166.7$, 135.6, 134.5, 127.1, 123.1, 122.4, 120.9, 120.2, 108.6, 41.0, 30.4, 26.0, 19.9, 15.1 ppm; IR (film): $\tilde{\nu}_{max} = 2963$, 2918, 2850, 1716, 1421, 1303 cm^{-1}; LRMS: *m/z* (%): 213 (59) [$M^{+\bullet}$], 198 (100), 182 (16), 170 (17), 153 (18), 77 (15); HRMS (ESI): *m/z* calcd for $[C_{14}H_{15}NO+H]^+$: 214.1232; found: 214.1213.

4-(1-Benzyl-4-ethyl-1*H*-indol-7-yl)-1,1-dibromopentan-2-one (40): Tetramethylpiperidine (TMP; 0.16 mL, 0.942 mmol, 2.7 equiv) was dissolved in anhydrous THF (1.5 mL) in a Schlenk flask and the solution was cooled to 0 °C. A 1.62 mol L^{-1} solution of *n*BuLi in hexanes (0.52 mL, 0.838 mmol, 2.4 equiv) was then added dropwise, whereupon the originally colorless solution turned yellow. After stirring for 30 min, this solution was added over a period of 20 min to a solution of ester **34** (117 mg, 0.349 mmol) in anhydrous THF (1.5 mL) containing CH_2Br_2 (0.061 mL, 0.873 mmol, 2.5 equiv) cooled to −78 °C. The mixture was stirred for 1 h and then poured into 1.2 mol L^{-1} aqueous HCl solution. The resulting mixture was extracted with EtOAc and the organic layer was washed with saturated aqueous $NaHCO_3$ solution, H_2O, and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexanes/EtOAc, 10:1) to afford **40** (103 mg, 0.216 mmol, 62%) as a yellow oil and recovered starting material (25 mg, 0.075 mmol, 21%). The reaction yield was 79% when considering only the reacted starting material. ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.29–7.17$ (m, 3H), 7.12 (d, $J = 3.0$ Hz, 1H), 6.98 (d, $J = 7.5$ Hz, 1H), 6.95–6.20 (m, 3H), 6.62 (d, $J = 3.0$ Hz, 1H), 5.68 (d, $J = 17.4$ Hz, 1H), 5.54 (s, 1H), 5.55 (d, $J = 17.4$ Hz, 1H), 3.91 (qdd, $J = 6.9$, 5.1, 2.1 Hz, 1H), 3.14 (dd, $J = 17.7$, 9.3 Hz, 1H), 3.49 (dd, $J = 17.7$, 9.3 Hz, 1H), 2.93 (q, $J = 7.5$ Hz, 2H), 1.36 (t, $J = 7.8$ Hz, 3H), 1.06 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 195.5$, 138.8, 134.7, 132.5, 131.2, 129.9, 128.8 (2C), 127.3, 127.2, 125.6 (2C), 119.8, 118.3, 100.0, 53.3, 44.1, 43.0, 28.7, 25.8, 21.4, 14.5 ppm; IR (film): $\tilde{\nu}_{max} = 2964$, 2930, 1724, 1503, 1454 cm^{-1}; LRMS: *m/z* (%): 303 (100) [$M^{+\bullet}$−172], 288 (60), 226 (30), 210 (13), 114 (17), 91 (53); HRMS (ESI): *m/z* calcd for $[C_{22}H_{24}Br_2NO+Na]^+$: 498.0044; found: 498.0035.

(*S*)-4-(1-Benzyl-4-ethyl-1*H*-indol-7-yl)pentanoic acid ((*S*)-42): A stirred solution of (*S*)-**35** (138 mg, 0.430 mmol) in anhydrous Et_2O (6.5 mL) was cooled to 0 °C. $BH_3{\cdot}SMe_2$ (0.082 mL, 0.860 mmol, 2 equiv) was then added dropwise, the mixture was allowed to warm to RT, and it was then heated at reflux for 5 h. It was then cooled to 0 °C once more and quenched by slowly adding H_2O. The aqueous phase was extracted with EtOAc, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography (hexanes/EtOAc, 8:2→7:3) to afford the corresponding alcohol (*S*)-3-(1-benzyl-4-ethyl-1*H*-indol-7-yl)butan-1-ol (127 mg, 0.413 mmol, 96%) as a colorless oil. This reaction proceeded equally well when THF was used instead of Et_2O and the reflux step was replaced by a longer reaction time (>12 h) at RT, giving the product in comparable yield. $[\alpha]_D^{25} = -10.4°$ ($c = 0.005\ g\,cm^{-3}$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.30–7.19$ (m, 3H), 7.08 (d, $J = 3.3$ Hz, 1H), 6.99–6.90 (m, 4H), 6.62 (d, $J = 3.3$ Hz, 1H), 5.67 (d, $J = 17.4$ Hz, 1H), 5.50 (d, $J = 17.4$ Hz, 1H), 3.43–3.25 (m, 3H), 2.94 (q, $J = 7.5$ Hz, 2H), 1.95–1.83 (m, 1H), 1.78–1.67 (m, 1H), 1.37 (t, $J = 7.5$ Hz, 3H), 1.09 ppm (d, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 139.4$, 134.0, 133.3, 130.8, 129.6, 128.8 (2C), 128.5, 127.3, 125.4 (2C), 119.6, 118.4, 100.0, 60.9, 53.1, 40.6, 29.0, 25.8, 23.1, 14.5 ppm; IR (film): $\tilde{\nu}_{max} = 3384$, 2963, 2929, 2871, 1502, 1553 cm^{-1}; LRMS: *m/z* (%): 307 (62) [$M^{+\bullet}$], 292 (6), 262 (83), 234 (40), 91 (100); HRMS (ESI): *m/z* calcd for $[C_{21}H_{25}NO+H]^+$: 308.2014; found: 308.2013. Anhydrous CH_2Cl_2 was added to a flask containing (*S*)-3-(1-benzyl-4-ethyl-1*H*-indol-7-yl)butan-1-ol (127 mg, 0.413 mmol) followed by pyridine (0.12 mL) and a catalytic amount of DMAP. Mesyl chloride (0.070 mL, 0.909 mmol, 2.2 equiv) was then added dropwise, whereupon the mixture became opaque. After stirring for 13 h at RT, H_2O was added and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O/EtOH (10:1) and brine/EtOH (10:1) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexanes/EtOAc, 8:2→7:3) to afford the mesylated product (*S*)-3-(1-benzyl-4-ethyl-1*H*-indol-7-yl)butyl methanesulfonate (150 mg, 0.390 mmol, 94%) as a light-yellow oil. $[\alpha]_D^{25} = -15.7°$ ($c = 0.005\ g\,cm^{-3}$ in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 7.31–7.20$ (m, 3H), 7.10 (d, $J = 3.3$ Hz, 1H), 6.94–6.90 (m, 4H), 6.62 (d, $J = 3.3$ Hz, 1H), 5.64 (d, $J = 17.4$ Hz, 1H), 5.48 (d, $J = 17.4$ Hz, 1H), 4.02–3.94 (m, 1H), 3.72–3.65 (m, 1H), 3.48–3.36 (m, 1H), 2.93 (q, $J = 7.5$ Hz, 2H), 2.66 (s, 3H), 2.12–1.90 (m, 1H), 1.36 (t, $J = 7.5$ Hz, 3H), 1.02 ppm (d, $J = 6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 138.9$, 134.4, 133.1, 131.0, 129.8, 128.8 (2C), 127.4, 127.0, 125.6 (2C), 119.4, 118.5, 100.0, 68.9, 53.3, 37.0, 36.6, 29.0, 25.8, 22.8, 14.5 ppm; IR (film): $\tilde{\nu}_{max} = 3029$, 2963,

2928, 2872, 2850, 1355, 1175 cm^{-1}; LRMS: *m/z* (%): 385 (42) [$M^{+\cdot}$], 289 (15), 274 (13), 262 (58), 167 (15), 91 (100); HRMS (ESI): *m/z* calcd for $[C_{22}H_{27}NO_3S+H]^+$: 386.1790; found: 386.1799. DMSO (1 mL) was added to a flask containing (*S*)-3-(1-benzyl-4-ethyl-1*H*-indol-7-yl)butyl methanesulfonate (71 mg, 0.185 mmol), followed by KCN (24 mg, 0.370 mmol, 2 equiv). The mixture was heated to 60 °C and stirred for 10 h, and then the reaction was quenched with H_2O. The resulting mixture was extracted with EtOAc, and the organic layer was washed with H_2O and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the remaining crude product was purified by flash chromatography (hexanes/EtOAc, 8:2) to afford (*S*)-4-(1-benzyl-4-ethyl-1*H*-indol-7-yl)pentanenitrile (48 mg, 0.152 mmol, 82 %) as a colorless oil. $[\alpha]_D^{25}=-5.5°$ ($c=0.005$ g cm^{-3} in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.31$–7.21 (m, 3H), 7.12 (d, $J=3.3$ Hz, 1H), 6.95–6.87 (m, 4H), 6.63 (d, $J=3.3$ Hz, 1H), 5.54 (d, $J=17.4$ Hz, 1H), 5.48 (d, $J=17.4$ Hz, 1H), 3.37–3.25 (m, 1H), 2.93 (q, $J=7.5$ Hz, 2H), 2.01–1.91 (m, 2H), 1.86–1.75 (m, 1H), 1.67–1.58 (m, 1H), 1.37 (t, $J=7.5$ Hz, 3H), 1.02 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=138.9$, 134.6, 133.2, 130.0, 128.9 (2C), 127.5, 126.3, 125.5 (2C), 120.1, 119.1, 118.6, 100.0, 53.4, 33.3, 21.1, 25.8, 23.0, 15.0, 14.4 ppm; IR (film): $\tilde{\nu}_{max}=3029$, 2964, 2930, 2871, 2246, 1502, 1454 cm^{-1}; LRMS: *m/z* (%): 316 (23) [$M^{+\cdot}$], 301 (3), 262 (21), 172 (9), 91 (100); HRMS (ESI): *m/z* calcd for $[C_{22}H_{24}N_2+H]^+$: 317.2018; found: 317.2015. A 20% aqueous solution (*w*/*w*) of KOH (7 mL) was added to a stirred solution of (*S*)-4-(1-benzyl-4-ethyl-1*H*-indol-7-yl)pentanenitrile (141 mg, 0.447 mmol) in ethylene glycol (7 mL), and the mixture was heated to 110 °C. After 12 h, the reaction mixture was cooled and slowly transferred to an extraction funnel containing 10 % aqueous HCl solution. The aqueous phase was extracted with EtOAc and the organic layer was washed with H_2O followed by saturated aqueous $NaHCO_3$ solution, then dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography (hexanes/EtOAc, 7:3→6:4→2:1) to furnish (*S*)-**42** (148 mg, 0.442 mmol, 98 %) as a light-brown oil. Comparable yields could be obtained in shorter reaction times (< 5 h) when the temperature was raised to 160 °C. $[\alpha]_D^{25}=-17.7°$ ($c=0.005$ g cm^{-3} in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.28$–7.18 (m, 3H), 7.08 (d, $J=3.2$ Hz, 1H), 6.97–6.87 (m, 4H), 6.62 (d, $J=3.2$ Hz, 1H), 5.55 (d, $J=17.3$ Hz, 1H), 5.47 (d, $J=17.3$ Hz, 1H), 3.29–3.18 (m, 1H), 2.93 (q, $J=7.7$ Hz, 2H), 2.07–1.91 (m, 2H), 1.87–1.73 (m, 2H), 1.37 (t, $J=7.7$ Hz, 3H), 1.09 ppm (d, $J=6.6$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=178.7$, 139.1, 134.1, 133.4, 130.8, 129.7, 128.9 (2C), 127.8, 127.4, 125.5 (2C), 119.4, 118.5, 100.1, 53.3, 32.3, 32.1, 31.7, 25.8, 23.1, 14.5 ppm; IR (film): $\tilde{\nu}_{max}=3786$, 3710, 2964, 2930, 2872, 2576, 1707, 1502, 1453 cm^{-1}; LRMS: *m/z* (%): 335 (50) [$M^{+\cdot}$], 262 (81), 234 (12), 156 (14), 91 (100); HRMS (ESI): *m/z* calcd for $[C_{22}H_{25}NO_2+H]^+$: 336.1964; found: 336.1959.

(*S*)-1-Benzyl-4-ethyl-8,9-dihydro-9-methyl-1*H*-benzo[*g*]indol-6(7*H*)-one ((*S*)-43): A nitrogen-purged flask containing acid (*S*)-**42** (55 mg, 0.164 mmol) was cooled to 0 °C. A solution of TFA (0.134 mL, 1.806 mmol, 11 equiv) and TFAA (0.843 mL, 6.068 mmol, 37 equiv) was then added dropwise under stirring, turning the light-brown starting material into a dark-purple slurry. After 5 min, a saturated solution of Na_2CO_3 was slowly added until the dark color of the mixture disappeared. The aqueous layer was extracted with EtOAc and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the resulting crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1→85:5→8:2) to afford (*S*)-**43** (27 mg, 0.085 mmol, 52 %) as a light-yellow oil. $[\alpha]_D^{25}=+201.8°$ ($c=0.005$ g cm^{-3} in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.74$ (s, 1H), 7.32–7.23 (m, 4H), 6.91–6.88 (m, 2H), 6.65 (d, $J=3.3$ Hz, 1H), 5.66 (d, $J=17.1$ Hz, 1H), 5.53 (d, $J=17.1$ Hz, 1H), 3.58–3.49 (m, 1H), 2.97–2.88 (m, 2H), 2.85–2.77 (m, 1H), 2.55 (ddd, $J=18.0$, 5.1, 2.1 Hz, 1H), 2.12 (tt, $J=13.8$ Hz, 4.8 Hz, 1H), 1.88 (ddt, $J=10.2$, 5.7, 2.4 Hz, 1H), 1.39 (d, $J=7.2$ Hz, 3H), 1.37 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=198.2$, 138.7, 134.6, 134.1, 133.7, 132.1, 129.0 (2C), 127.6, 126.6, 125.3 (2C), 117.4, 101.2, 52.9, 33.0, 29.1, 27.2, 25.8, 20.9, 14.3 ppm; IR (film): $\tilde{\nu}_{max}=3473$, 3031, 2964, 2930, 2870, 1664, 1497, 1453 cm^{-1}; LRMS: *m/z* (%): 317 (39) [$M^{+\cdot}$], 302 (26), 274 (5), 91 (100); HRMS (ESI): *m/z* calcd for $[C_{22}H_{23}NO+H]^+$: 318.1858; found: 318.1852.

(*S*)-4-Ethyl-8,9-dihydro-9-methyl-1*H*-benzo[*g*]indol-6(7*H*)-one ((*S*)-44): $AlCl_3$ (168 mg, 1.266 mmol, 6 equiv) was added to a solution of **43** (67 mg, 0.211 mmol) in anisole (2.5 mL), whereupon the mixture immediately turned dark green. It was stirred for 3 h at 100 °C, then cooled, and slowly transferred to an extraction funnel containing 10 % aqueous HCl solution. The aqueous phase was extracted with EtOAc and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. After evaporation of the solvent under vacuum, the crude product was purified by flash chromatography (hexanes/EtOAc, 9:1→8:2→7:3). The purified material was dissolved in HPLC grade MeCN (10 mg mL^{-1}), injected in 0.5 mL portions into a reversed-phase preparative HPLC setup (see the Supporting Information for details), and eluted with MeCN/H_2O (6:4) as the mobile phase to remove the benzyl migration products.[6a] The appropriate fractions were collected and extracted with EtOAc, and the organic layer was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure to afford (*S*)-**44** (19 mg, 0.082 mmol, 39 %) as a dark-brown oil. ^1H NMR (500 MHz, $CDCl_3$): $\delta=8.51$ (br s, 1H), 7.68 (s, 1H), 7.41 (dd, $J=3.0$, 2.5 Hz, 1H), 6.66 (dd, $J=3.0$, 2.0 Hz, 1H), 3.46–3.40 (m, 1H), 2.95–2.90 (m, 2H), 2.89–2.84 (m, 1H), 2.64 (ddd, $J=17.5$, 4.5, 3.0 Hz, 1H), 2.42 (tt, $J=13.5$, 5.0 Hz, 1H), 2.08 (ddt, $J=13.5$, 5.0, 2.5 Hz, 1H), 1.48 (d, $J=7.5$ Hz, 3H), 1.35 ppm (t, $J=7.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=198.1$, 134.8, 132.8, 131.5, 131.2, 127.1, 125.7, 116.6, 102.4, 33.5, 29.5, 28.1, 26.1, 18.6, 14.5 ppm; IR (film): $\tilde{\nu}_{max}=3311$, 2965, 2930, 2871, 1658, 1603 cm^{-1}; LRMS: *m/z* (%): 227 (97) [$M^{+\cdot}$], 212 (100), 199 (10), 184 (36), 168 (17), 156 (52); HRMS (ESI): *m/z* calcd for $[C_{15}H_{17}NO+H]^+$: 228.1388; found: 228.1379.

(*S*)-*tert*-Butyl 4-ethyl-6,7,8,9-tetrahydro-9-methyl-6-oxobenzo[*g*]indole-1-carboxylate ((*S*)-45): Anhydrous CH_2Cl_2 (1 mL) was added to a Schlenk flask containing the starting ketone (*S*)-**44** (19 mg, 0.083 mmol) followed by a catalytic amount of DMAP and Boc_2O (54 mg, 0.249 mmol, 3 equiv). The reaction mixture was stirred for 3 h and then H_2O was added. The resulting mixture was extracted with CH_2Cl_2 and the organic layer was washed with H_2O and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the remaining crude product was purified by flash chromatography (hexanes/EtOAc, 10:1) to afford (*S*)-**45** (26 mg, 0.080 mmol, 96 %) as a colorless oil. $[\alpha]_D^{25}=+200°$ ($c=0.005$ g cm^{-3} in $CHCl_3$); ^1H NMR (500 MHz, $CDCl_3$): $\delta=7.88$ (s, 1H), 7.67 (d, $J=3.7$ Hz, 1H), 6.64 (d, $J=3.7$ Hz, 1H), 4.23 (tdd, $J=7.0$, 6.5, 5.5 Hz, 1H), 2.87 (q, $J=7.5$ Hz, 2H), 2.78 (ddd, $J=16.5$, 4.5, 4.5 Hz, 1H), 2.64 (dddd, $J=16.5$, 4.5, 4.5, 4.5 Hz, 1H), 2.41–2.35 (m, 1H), 1.94–1.88 (m, 1H), 1.66 (s, 9H), 1.32 (t, $J=7.5$ Hz, 3H), 1.22 ppm (d, $J=6.5$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=199.1$, 149.4, 135.7, 135.6, 134.5, 132.8, 131.4, 129.4, 121.2, 105.6, 84.1, 34.9, 29.4, 28.0, 27.7, 25.6, 20.5, 14.7 ppm; IR (film): $\tilde{\nu}_{max}=2967$, 2933, 2872, 1747, 1679 cm^{-1}; LRMS: *m/z* (%): 227 (93) ([$M^{+\cdot}-100$]), 212 (100), 184 (37), 156 (54); HRMS (ESI): *m/z* calcd for $[C_{20}H_{25}NO_3+Na]^+$: 350.1732; found: 350.1727.

(*S*)-*tert*-Butyl 4-ethyl-8,9-dihydro-9-methylbenzo[*g*]indole-1-carboxylate ((*S*)-46): $NaBH_4$ (5 mg, 0.135 mmol, 2 equiv) was added to a solution of (*S*)-**45** (22 mg, 0.067 mmol) in MeOH (1 mL) at 0 °C. The mixture was allowed to warm to RT and cold H_2O was added after 30 min. The aqueous layer was extracted with EtOAc and the organic phase was washed with brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum, the crude residue was redissolved in anhydrous DMF (1.5 mL), and 85 % H_3PO_4 (0.161 mL, 2.765 mmol, 41 equiv) was added. The reaction mixture was then heated to 80 °C and stirred for 3.5 h. The temperature was then raised to 100 °C and stirring was continued for an additional 1 h. After cooling to RT, water was added and the resulting mixture was extracted with EtOAc. The organic layer was washed with saturated aqueous $NaHCO_3$ solution and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1) to afford (*S*)-**46** (16 mg, 0.051 mmol, 76 %) as a colorless oil. $[\alpha]_D^{25}=+96.0°$ ($c=0.005$ g cm^{-3} in $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): $\delta=7.51$ (d, $J=3.9$ Hz, 1H), 7.83 (s, 1H), 6.56 (d, $J=3.6$ Hz, 1H), 6.51 (dd, $J=9.6$, 3.0 Hz, 1H), 5.85 (ddd, $J=8.9$, 2.4Hz, 6.6 Hz, 1H), 4.14 (dq, $J=6.9$, 6.9 Hz, 1H), 2.82 (dq, $J=7.5$, 1.5 Hz, 2H), 2.67 (ddt, $J=17.4$, 6.9, 3.0 Hz, 1H), 2.21 (ddd, $J=17.4$, 6.3, 1.5 Hz, 1H), 1.63 (s, 9H), 1.29 (t, $J=$

7.5 Hz, 3H), 1.07 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=149.9$, 133.8, 133.2, 130.7, 130.1, 128.6, 128.2, 125.7, 124.5, 122.4, 105.4, 83.2, 30.8, 28.1 (3C), 27.0, 25.6, 20.0, 14.8 ppm; IR (film): $\tilde{\nu}_{max}=3034$, 2962, 2924, 2852, 1746, 1458, 1137 cm^{-1}; LRMS: *m*/*z* (%): 211 (79) [$M^{+\bullet}-100$], 196 (100), 180 (28), 167 (82), 152 (10), 90 (25); HRMS (ESI): *m*/*z* calcd for $[C_{20}H_{25}NO_2+Na]^+$: 334.1783; found: 334.1779.

(6*S*,8*S*)-*tert*-Butyl 4-ethyl-7,8-dihydro-6-(hydroxymethyl)-8-methylcyclopenta[*g*]indole-1(6*H*)-carboxylate (47): A solution of alkene (*S*)-**46** (40 mg, 0.129 mmol) in anhydrous MeCN (3 mL) was placed in a Schlenk flask filled with N_2 and cooled to −40 °C. TTN (63 mg, 0.141 mmol, 1.1 equiv) was added, the mixture was stirred for 5 min, and then $NaBH_4$ (20 mg, 0.529 mmol, 4.1 equiv) was added. The temperature was allowed to reach −20 °C (20 min) and the reaction was quenched by adding H_2O. The aqueous layer was extracted with EtOAc and the organic phase was washed with saturated aqueous NH_4Cl solution, H_2O, and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1→85:5→8:2) to afford **47** (21 mg, 0.064 mmol, 50%) as a colorless oil and recovered starting material (9 mg, 0.029 mmol, 22%). Considering only the reacted material, the reaction yield was 64%. $[\alpha]_D^{25}=+116.8°$ ($c=0.005$ g cm^{-3} in $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.50$ (d, $J=3.7$ Hz, 1H), 7.02 (s, 1H), 6.60 (d, $J=3.7$ Hz, 1H), 4.23 (tdd, $J=11.0$, 9.5, 3.0 Hz, 1H), 3.89 (ddd, $J=16.0$, 10.5, 5.0 Hz, 2H), 3.54 (dq, $J=7.5$, 2.0 Hz, 1H), 2.88 (q, $J=7.5$ Hz, 2H), 2.21 (dt, $J=12.5$, 8.0 Hz, 1H), 1.99 (ddd, $J=12.5$, 8.0, 3.0 Hz, 1H), 1.63 (s, 9H), 1.30 (t, $J=7.5$ Hz, 3H), 1.13 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=149.1$, 140.4, 135.1, 133.2, 131.8, 129.9, 126.3, 117.9, 105.7, 83.1, 66.6, 46.1, 36.7, 36.9, 28.1 (3C), 26.0, 22.0, 15.1 ppm; IR (film): $\tilde{\nu}_{max}=3420$, 2965, 2928, 2867, 1746, 1336, 1139 cm^{-1}; LRMS: *m*/*z* (%): 229(20) [$M^{+\bullet}-100$], 198 (100), 182 (18), 168 (64), 154 (35); HRMS (ESI): *m*/*z* calcd for $[C_{20}H_{27}NO_3+Na]^+$: 352.1889; found: 352.1886.

1,6,7,8-Tetrahydro-6-methylcyclopenta[*g*]indole (54): A solution of alkene **51**[26] (50 mg, 0.186 mmol) in anhydrous MeCN (3 mL) was placed in a Schlenk flask filled with N_2 and cooled to −40 °C. TTN (91 mg, 0.205 mmol, 1.1 equiv) was added, the mixture was stirred for 5 min, and then $NaBH_4$ (29 mg, 0.763 mmol, 4.1 equiv) was added. The temperature was allowed to reach −20 °C (20 min) and the reaction was quenched by adding H_2O. The aqueous layer was extracted with EtOAc and the organic phase was washed with saturated aqueous NH_4Cl solution and brine, and dried over anhydrous $MgSO_4$. The solvent was evaporated under vacuum and the crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1→8:2) to afford alcohol **52** (27 mg, 0.094 mmol, 51%) as a colorless oil. The alcohol **52** (17 mg, 0.059 mmol) was dissolved in CH_2Cl_2 (3.2 mL), and then Et_3N (0.5 mL) and TsCl (23 mg, 0.118 mmol, 2 equiv) were added. After about 3 h, the originally colorless mixture turned yellow. After stirring for 18 h at RT, H_2O was added and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine/EtOH (10:1) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the remaining crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1→8:2→7:3) to afford the corresponding tosylated compound **53** as a colorless oil in quantitative yield. This reaction was repeated to accumulate enough material. The tosylated product (19 mg, 0.043 mmol) was dissolved in DMSO (2 mL) and $NaBH_4$ (5 mg, 0.129 mmol, 3 equiv) was added. The mixture was heated to 80 °C and turned from colorless to yellow after a few hours. After stirring for 17 h, H_2O was added and the aqueous phase was extracted with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl solution and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1→8:2) to afford indole **54** (4 mg, 0.023 mmol, 53%) as a light-brown oil. ^{1}H NMR (500 MHz, $CDCl_3$): $\delta=7.95$ (br s, 1H), 7.50 (d, $J=8.0$ Hz, 1H), 7.16 (dd, $J=3.0$, 3.0 Hz, 1H), 7.02 (d, $J=8.0$ Hz, 1H), 6.56 (dd, $J=3.0$, 3.0 Hz, 1H), 3.35 (qdd, $J=7.0$, 7.0, 7.0 Hz, 1H), 3.07 (ddd, $J=15.5$, 9.0, 4.5 Hz, 1H), 2.94 (ddd, $J=15.0$, 8.0, 8.0 Hz, 1H), 2.45 (dddd, $J=16.0$, 8.0, 8.0, 4.0 Hz, 1H), 1.78–1.71 (m, 1H), 1.33 ppm (d, $J=7.0$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=143.1$, 132.8, 126.6, 124.8, 123.4, 118.8, 115.7, 103.1, 39.7, 34.8, 28.4, 20.8 ppm; IR (film): $\tilde{\nu}_{max}=3411$, 2954, 2924, 2865 cm^{-1}; LRMS: *m*/*z* (%): 171 (35) [$M^{+\bullet}$], 156 (100), 129 (21), 77 (29); HRMS (ESI): *m*/*z* calcd for $[C_{12}H_{13}N+H]^+$: 172.1126; found: 172.1119.

7-Ethyl-3*H*-pyrrolo[3,2,1-*ij*]quinolin-3-one (55): A 0.5 mol L^{-1} aqueous NaOH solution (0.18 mmol) was added to ester **36** (38 mg, 0.16 mmol) and the mixture was stirred for 10 h at RT. H_2O was then added to quench the reaction and the resulting mixture was extracted with EtOAc. The organic layer was washed with brine and dried over anhydrous $MgSO_4$, and the solvent was evaporated under vacuum. The crude product was purified by flash chromatography (hexanes/EtOAc, 7:3) to afford **55** (10 mg, 0.051 mmol, 32%) as a colorless oil. ^{1}H NMR (200 MHz, $CDCl_3$): $\delta=7.93$ (d, $J=3.8$ Hz, 1H), 7.79 (d, $J=9.4$ Hz, 1H), 7.52 (d, $J=7.9$ Hz, 1H), 7.23 (d, $J=7.9$ Hz, 1H), 6.92 (d, $J=3.8$ Hz, 1H), 6.64 (d, $J=9.4$ Hz, 1H), 3.00 (q, $J=7.7$ Hz, 2H), 1.35 ppm (t, $J=7.7$ Hz, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): $\delta=159.7$, 143.4, 138.8 (2C), 126.7, 124.8, 123.7, 123.0, 122.3, 115.2, 109.3, 26.7, 15.6 ppm; IR (film): $\tilde{\nu}_{max}=2964$, 2918, 1849, 1679, 1629, 1607 cm^{-1}; LRMS; *m*/*z* (%): 197 (47) [$M^{+\bullet}$], 182 (100).

(+)-*trans*-Trikentrin A: The starting alcohol **47** (9 mg, 0.027 mmol) was dissolved in CH_2Cl_2 (1.5 mL), and Et_3N (0.243 mL, 1.743 mmol, 64 equiv) and TsCl (10 mg, 0.054 mmol, 2 equiv) were added. After about 3 h, the originally colorless mixture turned yellow. After stirring for 18 h at RT, H_2O was added and the resulting mixture was extracted with CH_2Cl_2. The organic layer was washed with brine/EtOH (10:1) and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the remaining crude product was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1→8:2→7:3) to afford the corresponding tosylated compound as a colorless oil. This material was dissolved in DMSO (2 mL) and $NaBH_4$ (6 mg, 0.162 mmol, 6 equiv) was added. The reaction mixture was heated to 110 °C and turned from colorless to yellow after a few hours. After stirring for 43 h, H_2O was added and the aqueous phase was extracted with EtOAc. The organic layer was washed with saturated aqueous NH_4Cl solution and brine and dried over anhydrous $MgSO_4$. The solvent was evaporated under reduced pressure and the crude material was purified by flash chromatography (hexanes/EtOAc, 10:1→9:1) to afford (+)-*trans*-trikentrin A[6a] (4 mg, 0.019 mmol, 70% over two steps) as a brown oil. $[\alpha]_D^{25}=+24°$ ($c=0.00125$ g cm^{-3} in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.02$ (br s, 1H), 7.16 (dd, $J=2.9$, 2.6 Hz, 1H), 6.83 (s, 1H), 6.59 (dd, $J=3.3$, 2.0 Hz, 1H), 3.58–3.48 (m, 1H), 3.41 (ddq, $J=7.2$, 7.2, 6.9 Hz, 1H), 2.95 (q, $J=7.5$ Hz, 2H), 2.09–1.91 (m, 2H), 1.36 (t, $J=7.5$ Hz, 3H), 1.33 (d, $J=6.9$ Hz, 3H), 1.30 ppm (d, $J=6.9$ Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): $\delta=142.5$, 135.1, 132.1, 127.2, 126.1, 122.8, 114.1, 101.5, 43.8, 37.9, 36.0, 26.5, 20.8, 20.0, 15.0 ppm; IR (film): $\tilde{\nu}_{max}=3415$, 2960, 2925, 2667, 1260, 1094, 1026, 901 cm^{-1}; LRMS: *m*/*z* (%): 213 (46) [$M^{+\bullet}$], 198 (100), 184 (14), 169 (29), 154 (14); HRMS (ESI): *m*/*z* calcd for $[C_{15}H_{19}N+H]^+$: 214.1596; found: 214.1581.

Acknowledgements

The authors wish to thank the CNPq, FAPESP, and CAPES for financial support, and Professor L. H. Andrade (USP) and Professor R. O. M. A. Sousa (UFRJ) for fruitful discussions and for providing the enzymes. S. Lazar (AmanoEnzyme-USA) is acknowledged for providing a sample of PS-IM. Dr. M. Schrems and Prof. A. Pfaltz (University of Basel) are acknowledged for their help during the asymmetric hydrogenations and for kindly providing the catalysts.

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Received: July 6, 2012
Revised: September 4, 2012
Published online: November 4, 2012

