DOI: 10.1002/ejoc.200901404

First Asymmetric Synthesis of Boehmeriasin A

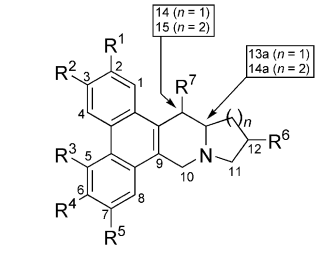
David Dumoulin,[a,b,c] Stéphane Lebrun,[a,b,c] Axel Couture,*[a,b,c] Eric Deniau,[a,b,c] and Pierre Grandclaudon[a,b,c]

Keywords: Nucleophilic addition / Diastereoselectivity / Cyclization / Ring-closing metathesis / Total synthesis

The first asymmetric synthesis of phenanthroquinolizidine alkaloid (*R*)-boehmeriasin A is described. Two alternative synthetic pathways to the key intermediate (*RS*,*R*)-**4** were achieved through a combination of highly diastereoselective 1,2-nucleophilic addition on (–)-(*S*)-1-amino-2-(methoxymethyl)pyrrolidine hydrazones with a ring-closing metathesis to ensure the construction of the piperidine template. A subsequent acylation/oxidation/aldol condensation/radical cyclization sequence completed the assembly of the title (*R*)-configured natural product.

Introduction

Since the first isolation of tylophorine in 1935 from the perennial climbing plant *Tylophoria indica*,[1] the class of phenanthroizidine alkaloids has grown considerably; it presently encompasses close to 70 structurally related models.[2] The defining feature of these pentacyclic natural products, which are found primarily in plants belonging to the *Asclepiadaceae*, *Moraceae*, *Lauraceae* and *Urticaceae* families,[2a] is the presence of a highly oxygenated phenanthrene ring fused to a saturated N-heterocycle (Figure 1).



Cryptopleurine (**1a**)
$n = 2$; $R^1 = R^2 = R^4 = MeO$
$R^3 = R^5 = R^6 = R^7 = H$

Cryptopleuridine (**1b**)
$n = 2$; $R^1 = R^2 = OCH_2O$; $R^4 = MeO$
$R^3 = R^5 = R^7 = H$; $R^6 = OH$

Hydroxycryptopleurine (**1c**)
$n = 2$; $R^1 = R^2 = R^4 = MeO$
$R^3 = R^5 = R^6 = H$; $R^7 = OH$

Boehmeriasin A (**1d**)
$n = 2$; $R^2 = R^4 = R^5 = MeO$
$R^1 = R^3 = R^6 = R^7 = H$

Boehmeriasin B (**1e**)
$n = 2$; $R^2 = R^5 = MeO$; $R^4 = OH$
$R^1 = R^3 = R^6 = R^7 = H$

Figure 1. Structures of phenanthroindolizidines and phenanthroquinolizidines.

[a] Université Lille Nord de France,
59000 Lille, France
Fax: +33-3-20336309
E-mail: axel.couture@univ-lille1.fr
[b] USTL, Laboratoire de Chimie Organique Physique, Bâtiment C3(2),
59655 Villeneuve d'Ascq, France
[c] CNRS, UMR 8009 "COM",
59655 Villeneuve d'Ascq, France

Phenanthroizidines exhibit interesting biological properties, especially profound cytotoxic activity, and have been shown to provide other medicinal benefits including mitotic, antileukemic, antimoebic, antibacterial and antibiotic activities; such compounds have also been used as insecticides and insect antifeedants.[2,3] In addition, analogues of these natural products have been prepared and subjected to various forms of biological screening.[2a,4]

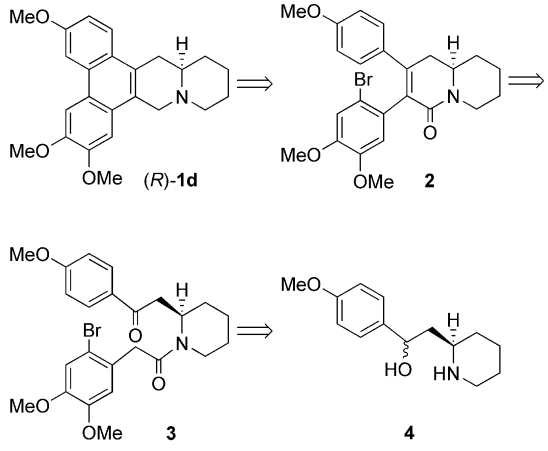
As a consequence of their promising biological profile, coupled with their low natural abundance and unusual architecture, the phenanthrolizidine alkaloids have engendered an impressive number of synthetic studies for the purpose of fundamental research and drug development. However, most of these racemic and asymmetric synthetic studies[2a,2b,5] have been devoted to the indolizidines, which are much more prevalent than the corresponding quinolizidines in natural sources. Despite the fact that the closely related phenanthroquinolizidine alkaloids exert interesting antiviral, antifungal, antimicrobial and cancerostatic effects, as well as inhibiting proteosynthesis in eukaryotic cells,[2a,5e] they have received less attention as potential therapeutic leads and have not elicited the same synthetic efforts.[2a,5a] This is probably due to the fact that cryptopleurine (**1a**), which was isolated as early as 1948 from the bark of *Cryptocarya pleurosperma*,[6] was deemed for a long time to be the sole example of this exceedingly rare class of alkaloids. This family was later enriched by isolation of the hydroxy derivatives cryptopleuridine (**1b**)[7] and 15-hydroxycryptopleurine (**1c**),[8] and by the recent extraction of boehmeriasin A (**1d**) and B (**1e**) from the aqueous ethanolic extract of *Boehmeria siamensis* Craib (*Urticaceae*) by bioassay-guided fractionation.[9] In assays for cytotoxicity on a panel of twelve cancer cell lines, which included leukemia and cancers of the kidney, prostate, lung and breast, boehmeriasin A proved to be more potent than Paclitaxel, with IC_{50} values in the low nanomolar range.[10] Whereas several synthetic methodologies have been developed for the elabora-

tion of cryptopleurine and its hydroxy derivatives in both racemic and optically active forms[5] in order to determine chemical structure and stereochemistry, only one example of a racemic approach to boehmeriasin A has been reported.[5a]

In this paper we wish, therefore, to describe for the first time a flexible, asymmetric synthesis of the representative phenanthroquinolizidine alkaloid boehmeriasin A (**1d**). Our main objective was to ensure that the synthetic methodology allowed optimization of the pharmacological profiles of these potent cytotoxic agents through simple modification of their basic skeleton to enable a range of analogues of this alkaloid to be prepared efficiently.

Results and Discussion

The retrosynthetic analysis of **1d** is shown in Scheme 1. The pentacyclic skeleton of the (*R*)-configured alkaloid could be constructed by radical-induced annulation of the *ortho*-bromostilbene derivative **2**, which could be assembled by intramolecular aldol-type condensation of the oxo amide **3**. The cyclization precursor should be accessible from the amino alcohol **4**, and this key intermediate was, in turn, envisioned to arise from a strategic combination of the highly diastereoselective nucleophilic 1,2-addition on chiral (–)-(*S*)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP) hydrazones[11] and subsequent acylation with acryloyl chloride with a ring-closing metathesis.[12]

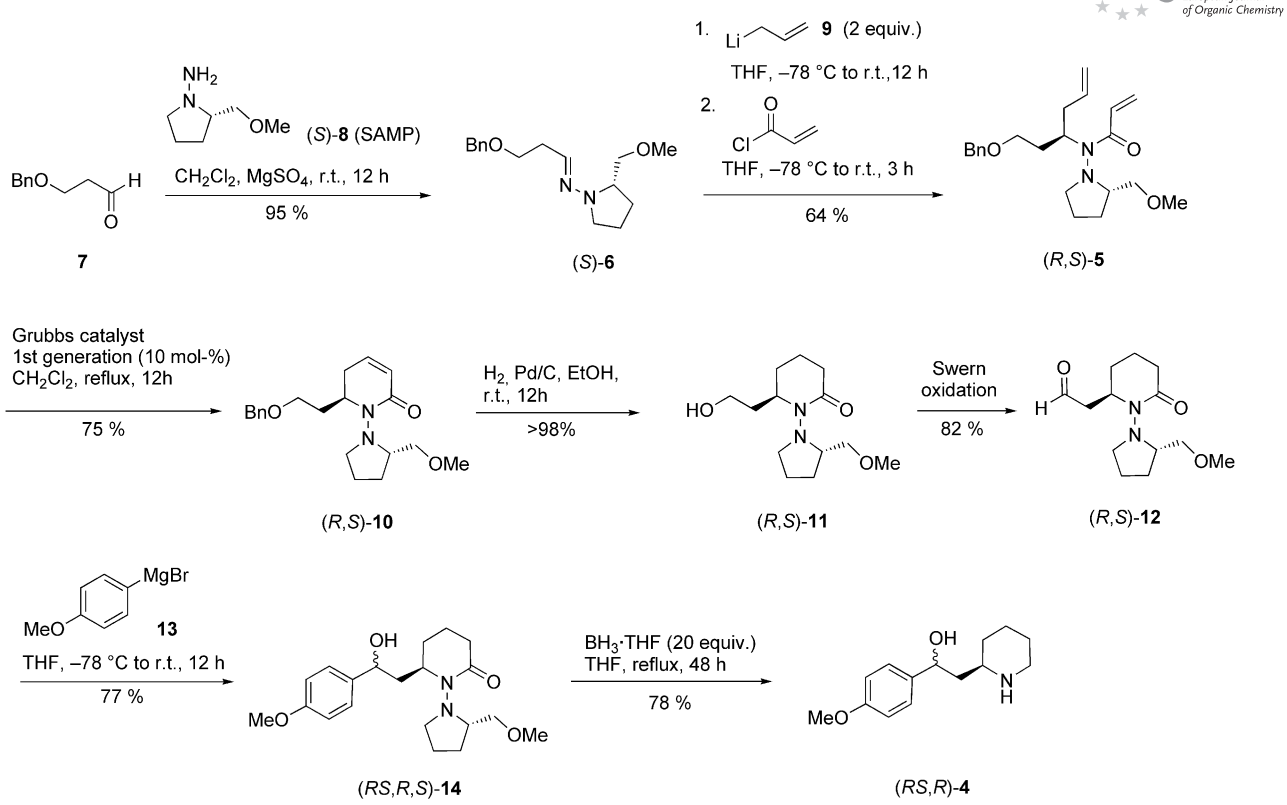


Scheme 1. Retrosynthetic analysis.

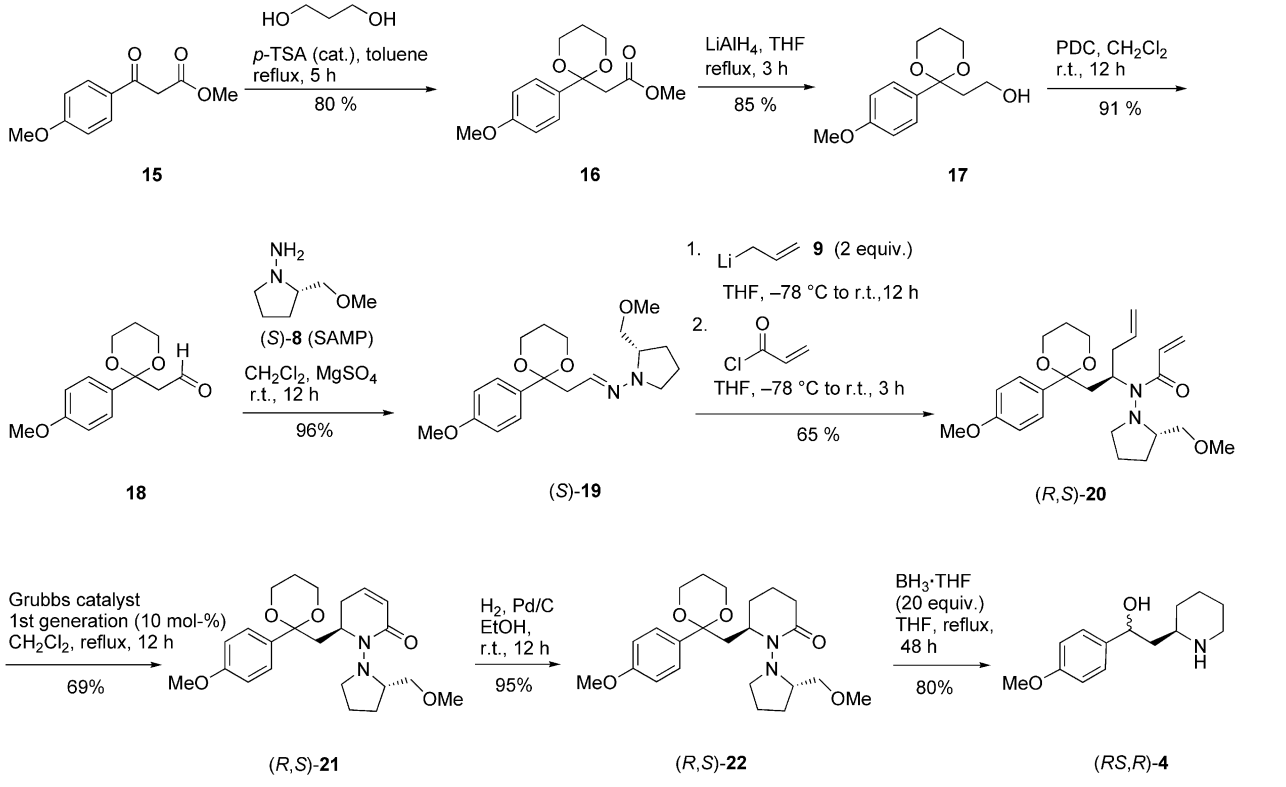
For the elaboration of amino alcohol **4**, we set out to achieve alternative strategies to secure the stereochemistry of the hydroxyalkyl appendage on the piperidine template. The two approaches differed in the stage at which the chiral center is introduced. Initially, the synthetic route portrayed in Scheme 2 was developed. The first facet of the synthesis was the assembly of the highly conjugated precursor diene hydrazide **5**, which was performed as a single one-pot reaction from chiral SAMP hydrazone **6**. The synthesis started from the benzyl-protected 3-hydroxypropionaldehyde (**7**), which was quantitatively converted into the enantiopure SAMP hydrazone (*S*)-**6** by simply mixing with enantiomerically pure hydrazine (–)-(*S*)-1-amino-2-(methoxymethyl)-pyrrolidine [(*S*)-**8**]. Hydrazone (*S*)-**6** was submitted to an addition reaction with allyllithium (**9**), and the intermediate lithium hydrazide salt was intercepted with acryloyl chloride to give straightforward access to the desired diene hydrazide (*R*,*S*)-**5**. This polyene compound was obtained with satisfactory yield; NMR spectroscopic investigations after chromatographic separation indicated the presence of a single diastereomer, thus confirming the high level of diastereoselectivity observed upon the initial 1,2-nucleophilic addition process on the C=N double bond.[11a] This procedure allowed the absolute configuration at the C-14a carbon atom in the final compound **1d** to be introduced in a defined manner, which is one of the major challenges in the total synthesis of the target alkaloid. Ring-closing metathesis using first-generation Grubbs catalyst [$Cl_2Ru(=CHPh)(PCy_3)_2$, 10 mol-%)] in refluxing CH_2Cl_2, proceeded smoothly to provide a satisfactory yield of the virtually diastereochemically pure cyclic ene hydrazide (*R*,*S*)-**10**. Catalytic hydrogenation with concomitant release of the benzyl protection of the 2-hydroxyethyl group proceeded uneventfully to afford the hydroxyalkylated hydrazide (*R*,*S*)-**11** in excellent yield and high diastereoselectivity (*de* ≥ 96%). Subsequent Swern oxidation of **11** delivered the cyclic hydrazide (*R*,*S*)-**12** with the aldehyde functionality necessary to secure the ultimate installation of the hydroxybenzyl appendage. Compound (*R*,*S*)-**12** was then allowed to react with the appropriate Grignard reagent **13** and standard workup delivered the hydroxylated hydrazide **14** in excellent yield as a 1:1 mixture of diastereomeric (*R*,*R*,*S*)/(*S*,*R*,*S*) compounds.

At this stage, stereochemical considerations of the benzylic carbon centre were not crucial for the outcome of the synthetic process, because conversion of the benzylic hydroxy functionality into a carbonyl group was planned at a later stage of the sequence. Finally, the reductive bond cleavage of **14** with BH_3·THF was accomplished through simultaneous reduction of the lactam carbonyl functionality to complete the synthesis of the key intermediate amino alcohol (*RS*,*R*)-**4**. The overall yield for the formation of this piperidine derivative following the synthetic route depicted in Scheme 2 was 17% over eight steps. We surmised that the efficiency of the process could be significantly improved by using an alternative strategy based upon the incorporation of the aromatic unit prior to installation of the stereodefined hydroxyalkyl appendage on the piperidine template.

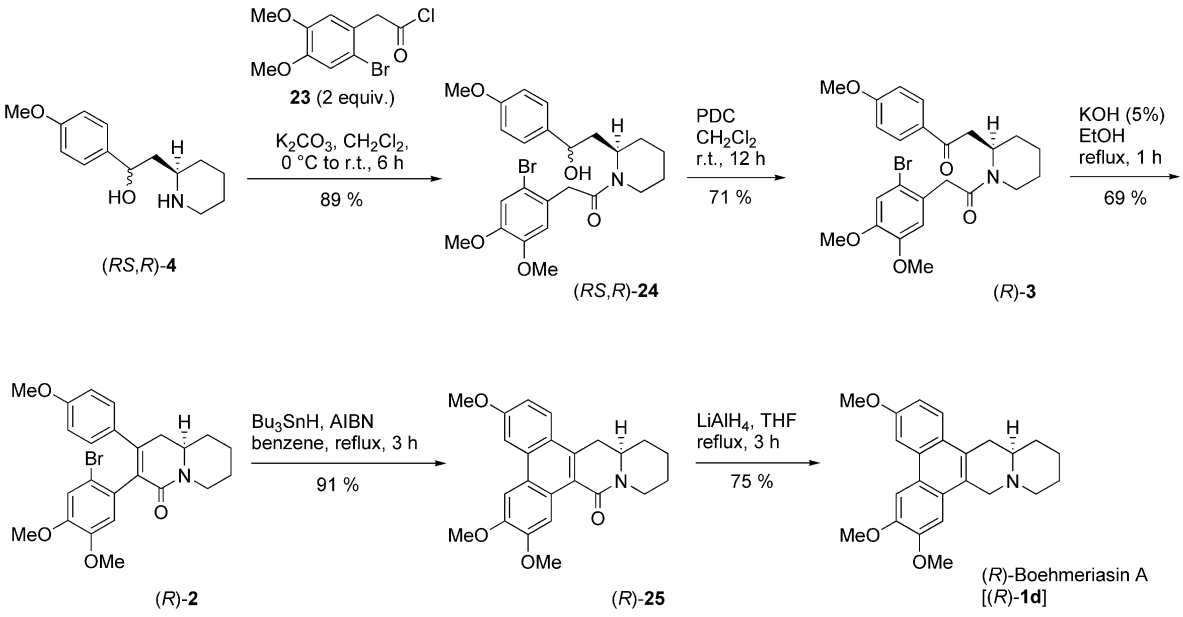
In this second approach, we embarked on the synthesis of key intermediate **4** using the route depicted in Scheme 3, starting from aromatic oxo ester **15**. Acetal protection, followed by a reduction/oxidation sequence applied to **16** and **17**, respectively, delivered the protected carbaldehyde **18**, which was then coupled with enantiopure hydrazine (*S*)-**8** to provide an excellent yield of hydrazone (*S*)-**19**. Sequential treatment with allyllithium (**9**) and trapping with acryloyl chloride, as described in Scheme 2, afforded diolefinic hydrazide (*R*,*S*)-**20** as a single diastereoisomer (*de* ≥ 96%), which was characterized by its NMR spectra after chroma-



Scheme 2. Synthesis of key intermediate amino alcohol **4**.



Scheme 3. Alternative synthesis of key amino alcohol **4**.



Scheme 4. Asymmetric synthesis of (*R*)-boehmeriasin A.

tographic treatment. This bis(olefin) was then subjected to ring-closing metathesis, which delivered an excellent yield of the diastereochemically pure cyclic ene hydrazide (*R*,*S*)-**21**. Catalytic hydrogenation of the olefinic double bond proceeded smoothly to afford the corresponding saturated hydrazide (*R*,*S*)-**22** in excellent yield and high diastereoselectivity. The choice of the acetal protection was rewarded here, because treatment of (*R*,*S*)-**22** with the BH_3·THF complex, followed by standard basic workup, triggered three simultaneous operations: release of the temporary chiral auxiliary, reduction of the lactam carbonyl functionality and stereocontrolled installation of the hydroxyalkyl appendage, to provide a 1:1 diastereomeric mixture of (*R*,*R*)- and (*S*,*R*)-**4**. This compound was obtained with an overall yield of 21% over eight steps, thus demonstrating that the second synthetic approach to key intermediate **4** shown in Scheme 3 is more efficient and appealing than the former. Interestingly, because the olefinic moieties of **10** and **21** and the metalation sites in **11** and **22** are all present in intermediate compounds equipped with a stereocontrolling agent, such compounds could serve as key branching points for alternative functionalization chemistries; this should enable the pharmacological profile of the target compounds to be optimized.

With amino alcohol **4** in hand, we set out to assemble the title compound **1d** using Kibayashi's method for the synthesis of (–)-(*R*)-cryptopleurine[5g,5h] as depicted in Scheme 4. Acylation of (*RS*,*R*)-**4** with the appropriate bromobenzoyl chloride **23** produced an excellent yield of the hydroxy amide (*RS*,*R*)-**24**, which was subsequently oxidized with pyridinium dichromate (PDC) to provide a fairly good yield of virtually enantiopure oxo amide (*R*)-**3** – a suitable candidate for the elaboration of the quinolizidine scaffold. Intramolecular aldol-type condensation under basic conditions[13] led to the formation of quinolizidinone (*R*)-**2**, which contained a bromostilbene unit embedded in the compact annulated compound framework. Construction of the phenanthrene nucleus was achieved by treatment with Bu_3SnH and AIBN, which effected a very efficient intramolecular radical cyclization.[14] Finally, reduction of pentacyclic lactam (*R*)-**25** with $LiAlH_4$ completed the synthesis of the title compound boehmeriasin A [(*R*)-**1d**], which was obtained in 29% overall yield (over the last five steps). The enantiopurity of the synthetic (*R*)-boehmeriasin A was clearly established from the sign and value of the specific optical rotation and from spectroscopic data, which matched those reported for the natural product {$[a]_D^{25}$ = –80.2 (*c* = 0.15, CH_3OH); ref.[9] $[a]_D^{25}$ = –80.4 (*c* = 0.1, CH_3OH)}. Furthermore, our asymmetric synthetic route allowed the assignment of the (*R*) absolute configuration to the recently isolated natural product.

Conclusions

We have devised a new and flexible method for the first asymmetric synthesis of (+)-(*R*)-boehmeriasin A. The key step is the elaboration of a chiral building block, which was assembled following two synthetic routes based upon strategic combinations of a highly diastereoselective 1,2-nucleophilic addition/acylation process applied to an enantiopure SAMP hydrazone with a ring-closing metathesis reaction to form the piperidine template. The main advantages of this synthetic method lie in the formation of chiral saturated or unsaturated hydrazide intermediates that could be exploited for further synthetic use. Such compounds could be further functionalized, for example by epoxidation and dihydroxylation, which could have an impact on the biological profile of target models. Finally, the synthetic strategy has significant potential for further extension to a range

of analogues in this series and to the antipode of the natural product owing to the availability of the RAMP chiral auxiliary.

Experimental Section

General Methods: Tetrahydrofuran (THF) was pre-dried with anhydrous Na_2SO_4 and distilled from sodium benzophenone ketyl under argon before use. CH_2Cl_2, Et_3N, and toluene were distilled from CaH_2. Dry glassware was obtained by oven-drying and assembly under dry argon. The glassware was equipped with rubber septa, and reagent transfer was performed by using syringe techniques. Merck silica gel 60 (40–63 μm; 230–400 mesh ASTM) was used for flash chromatography. Melting points were obtained with a Reichert–Thermopan apparatus. Optical rotations were measured with a Perkin–Elmer 343 polarimeter. Elemental analyses were obtained with Carlo–Erba CHNS-11110 equipment. NMR spectra were recorded with a Bruker AM 300 (300 MHz and 75 MHz, for ^1H and ^{13}C, respectively) by using $CDCl_3$ as solvent and TMS as internal standard. Oxo ester **15** is commercially available. 3-(Benzyloxy)propionaldehyde (**7**)[15] and (3-benzyloxypropylidene)[(2*S*)-2-methoxymethylpyrrolidin-1-yl]amine (**6**)[16] were prepared according to reported procedures. 2-Bromo-4,5-dimethoxyphenylacetyl chloride (**23**)[17] was synthesized following literature methods.

***N*-[(1*R*)-1-(2-Benzyloxyethyl)but-3-enyl]-*N*-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]acrylamide (5):** Phenyllithium (1.8 M in dibutyl ether, 2 mL, 3.7 mmol) was added dropwise to a solution of allyltriphenyltin (1.46 g, 3.7 mmol) in dry THF (10 mL) under argon. After stirring at room temp. for 30 min, the suspension was cooled to –78 °C, and a solution of hydrazone **6** (500 mg, 1.81 mmol) in dry THF (3 mL) was added dropwise by syringe. The mixture was stirred at –78 °C for 30 min, then allowed to warm to room temp. and stirred for an additional 12 h. The mixture was re-cooled to –78 °C, and acryloyl chloride (524 mg, 0.47 mL, 5.79 mmol) was added dropwise. After stirring at –78 °C for 30 min, the mixture was allowed to warm to room temp. over 3 h. Water (10 mL) was added dropwise, and the mixture was filtered and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), the solvent was removed under vacuum, and the oily residue was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 30:70) to afford the diene hydrazide **5** as a yellow oil (431 mg, 64%). $[a]_D^{25}$ = –16.3 (*c* = 4.50, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.63–1.92 (m, 4 H, 2 × CH_2), 2.21–2.24 (m, 2 H, CH_2), 2.72 (t, *J* = 7.2 Hz, 2 H, CH_2), 2.88–2.93 (m, 2 H, CH_2), 3.19–3.34 [m, 6 H (1 H and 5 H), CH_2OCH_3], 3.41–3.48 (m, 1 H, NCH), 3.52 (t, *J* = 5.7 Hz, 2 H, OCH_2), 4.43 (d, J_{AB} = 11.8 Hz, 1 H, OCH_2Ph), 4.54 (d, J_{AB} = 11.8 Hz, 1 H, OCH_2Ph), 4.98–5.12 (m, 2 H, CH_2=), 5.55 (dd, *J* = 2.3, 10.5 Hz, 1 H, CH_2=), 5.75–5.82 (m, 1 H, CH_2=), 6.27 (dd, *J* = 2.3, 17.2 Hz, 1 H, CH_2=), 7.15 (dd, *J* = 10.5, 17.2 Hz, 1 H, COCH=), 7.24–7.31 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.5 (CH_2), 26.3 (CH_2), 33.3 (CH_2), 37.4 (CH_2), 52.1 (NCH_2), 53.2 (CH), 58.1 (CH), 58.9 (OCH_3), 67.4 (CH_2), 72.7 (CH_2), 74.2 (CH_2), 117.1 (CH_2=), 126.1 (CH_2=), 127.5 (2 × CH), 128.7 (2 × CH), 129.4 (CH), 135.9 (CH), 137.2 (CH), 138.5 (C), 169.5 (CO) ppm. $C_{22}H_{32}N_2O_3$ (372.5): calcd. C 70.94, H 8.66, N 7.32; found C 71.07, H 8.48, N 7.59.

(6*R*)-6-(2-Benzyloxyethyl)-1-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-5,6-dihydro-1*H*-pyridin-2-one (10): Grubbs first-generation catalyst (0.3 g, 10 mol-%, 0.37 mmol) was added to a stirred solution of diene hydrazide **5** (1.4 g, 3.76 mmol) in dry CH_2Cl_2 (80 mL), and the resulting mixture was refluxed for 12 h. Then, the mixture was concentrated under reduced pressure, and the oily residue was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 55:45) to afford the ene hydrazide **10** as a yellow oil (971 mg, 75%). $[a]_D^{25}$ = –32.5 (*c* = 0.50, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.44–1.52 (m, 1 H, CH_2), 1.71–1.78 (m, 1 H, CH_2), 1.97–2.22 (m, 4 H, 2 × CH_2), 2.34 (dd, *J* = 2.3, 3.5 Hz, 1 H, CH_2), 2.68 (dd, *J* = 2.6, 6.8 Hz, 1 H, CH_2), 3.12–3.16 (m, 1 H, NCH_2), 3.31 (s, 3 H, OCH_3), 3.35–3.39 (m, 2 H, OCH_2), 3.50 (t, *J* = 6.1 Hz, 2 H, OCH_2), 3.59–3.67 (m, 1 H, NCH), 3.75–3.88 [m, 2 H (1 H, NCH, 1 H, NCH_2)], 4.42 (d, J_{AB} = 11.8 Hz, 1 H, OCH_2Ph), 4.51 (d, J_{AB} = 11.8 Hz, 1 H, OCH_2Ph), 5.80 (dd, *J* = 2.6, 9.8 Hz, 1 H, CH=), 6.34 (t, *J* = 8.2 Hz, 1 H, CH=), 7.28–7.35 (m, 5 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (CH_2), 27.4 (CH_2), 28.6 (CH_2), 32.1 (CH_2), 52.8 (NCH), 58.9 (OCH_3), 59.9 (CH), 60.6 (CH), 67.4 (CH_2), 72.9 (CH_2), 76.5 (CH_2), 125.9 (CH=), 127.4 (2 × CH), 128.4 (2 × CH), 129.1 (CH), 137.2 (CH=), 138.2 (C), 162.9 (CO) ppm. $C_{20}H_{28}N_2O_3$ (344.5): calcd. C 69.74, H 8.19, N 8.13; found C 69.78, H 8.45, N 7.99.

(6*R*)-6-(2-Hydroxyethyl)-1-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]-piperidin-2-one (11): A solution of ene hydrazide **10** (580 mg, 1.69 mmol) in EtOH (15 mL) was stirred with activated Pd/C (10%, 10 mg) at room temp. under H_2 (1 atm) until TLC indicated complete consumption of the starting material (12 h). The mixture was filtered through a pad of Celite, which was further eluted with EtOH (30 mL) and CH_2Cl_2 (30 mL). The filtrate was concentrated under reduced pressure, and the resulting crude product was purified by flash column chromatography on silica gel (ethyl acetate) to afford **11** as a colorless oil (429 mg, 99%). $[a]_D^{25}$ = –74.6 (*c* = 2.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.48–1.80 (m, 6 H, 3 × CH_2), 1.84–2.13 (m, 4 H, 2 × CH_2), 2.35 (t, *J* = 6.8 Hz, 2 H, CH_2CO), 3.08–3.19 (m, 1 H, NCH_2), 3.29–3.35 (m, 5 H, OCH_3, OCH_2), 3.52–3.63 [m, 2 H (1 H, NCH, 1 H, NCH_2)], 3.70–3.85 (m, 3 H, OCH_2, NCH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.6 (CH_2), 23.0 (CH_2), 27.2 (CH_2), 29.8 (CH_2), 34.1 (CH_2), 37.8 (CH_2), 53.1 (NCH_2), 58.7 (OCH_3), 59.8 (CH), 60.2 (CH_2OH), 60.8 (CH), 75.2 (CH_2O), 169.2 (CO) ppm. $C_{13}H_{24}N_2O_3$ (256.4): calcd. C 69.39, H 9.44, N 10.93; found C 69.49, H 9.27, N 10.74.

{(2*R*)-1-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-6-oxopiperidin-2-yl}acetaldehyde (12): A solution of DMSO (368 mg, 0.33 mL, 4.72 mmol) in CH_2Cl_2 (2 mL) was slowly added to a stirred solution of oxalyl chloride (273 mg, 0.19 mL, 2.15 mmol) in CH_2Cl_2 (5 mL) at –78 °C. The mixture was stirred at –78 °C for 30 min, and then a solution of alcohol **11** (550 mg, 2.15 mmol) in CH_2Cl_2 (2 mL) was added dropwise. After 30 min, Et_3N (1.08 g, 1.5 mL, 10.7 mmol) was added, and the stirred mixture was allowed to warm to room temp. over 2 h. Water (15 mL) was added, and the aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under vacuum. The oily residue was purified by flash column chromatography on silica gel (ethyl acetate) to afford aldehyde derivative **12** as a yellow oil (448 mg, 82%). $[a]_D^{25}$ = +1.7 (*c* = 0.70, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.29 (m, 1 H, CH_2), 1.38–1.47 (m, 2 H, CH_2), 1.53–1.59 (m, 1 H, CH_2), 1.66–1.82 (m, 2 H, CH_2), 1.87–1.98 (m, 2 H, CH_2), 2.23–2.34 (m, 4 H, $NCOCH_2$, CH_2CO), 2.67 (dt, *J* = 4.1, 7.9 Hz, 1 H, NCH_2), 3.23 (d, *J* = 5.4 Hz, 2 H, CH_2O), 3.26 (s, 3 H, OCH_3), 3.29–3.34 (m, 1 H, NCH_2), 3.85–3.88 (m, 1 H, NCH), 4.33–4.38 (m, 1 H, NCH), 9.53 (t, *J* = 3.1 Hz, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.2 (CH_2), 22.5 (CH_2), 27.0 (CH_2), 30.4 (CH_2), 34.2 (CH_2), 49.7 (CH_2), 52.0 (NCH_2), 58.4 (OCH_3), 58.6 (CH), 59.8 (CH), 76.3 (OCH_2), 168.7 (CO), 195.2 (CHO) ppm. $C_{13}H_{22}N_2O_3$ (254.3): calcd. C 61.43, H 8.72, N 11.01; found C 61.72, H 8.89, N 10.78.

(6*R*)-6-[(2*RS*)-2-Hydroxy-2-(4-methoxyphenyl)ethyl]-1-[(2*S*)-2-(methoxymethyl)pyrrolidin-1-yl]piperidin-2-one (14): A solution of *p*-

methoxybenzylmagnesium bromide (1 M in THF, 1.73 mL, 1.73 mmol) was slowly added to a solution of aldehyde **12** (400 mg, 1.57 mmol) in dry THF (10 mL) at –78 °C under argon. After stirring at –78 °C for 2 h, the reaction mixture was allowed to warm to room temp. over 12 h and then quenched with saturated aqueous $NaHCO_3$ (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic layers were washed with brine (10 mL) and dried ($MgSO_4$). Evaporation of the solvent under reduced pressure left a residue, which was purified by column chromatography on silica gel (ethyl acetate) to afford **14** as an inseparable 1:1 mixture of (*R*,*R*,*S*)/(*S*,*R*,*S*) isomers (423 mg, 77%). The isomeric ratio was evaluated from the ^1H NMR spectrum and integration of the C*H*OH protons: δ = 4.68 (dd, *J* = 5.3, 7.6 Hz, 1 H) and 4.89 (dd, *J* = 2.5, 10.8 Hz, 1 H) ppm.

(1*RS*)-1-(4-Methoxyphenyl)-2-[(2*R*)-piperidin-2-yl]ethanol (4): BH_3·THF (1 M in THF, 22.1 mL, 22.1 mmol) was slowly added to a solution of **14** (400 mg, 1.1 mmol) in dry THF (15 mL) at 0 °C. After refluxing for 48 h, the reaction mixture was cooled to room temp. and quenched with aqueous NaOH (10%, 10 mL). The mixture was concentrated under vacuum to one-third of its volume and refluxed for 5 h. The aqueous layer was separated and extracted with Et_2O (3 × 30 mL). The combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure to afford a 1:1 mixture of amino alcohols (*R*,*R*,*S*)-**4**/(*S*,*R*,*S*)-**4** (combined yield: 202 mg, 78%), which was used directly in the next step without further purification. The isomeric ratio was evaluated from the ^1H NMR spectrum and integration of the C*H*OH protons: δ = 4.84 (dd, *J* = 3.2, 9.8 Hz, 1 H) and 4.93 (dd, *J* = 4.2, 7.3 Hz, 1 H) ppm.

Methyl [2-(4-Methoxyphenyl)[1,3]dioxan-2-yl]acetate (16): A stirred solution of β-oxo ester **15** (16.0 g, 77 mmol) in dry toluene (60 mL), 1,3-propanediol (17.6 g, 0.231 mmol) and a catalytic amount of *p*-touenesulfonic acid was subjected to azeotropic distillation by using a Dean–Stark trap for 5 h. The solvent was evaporated under reduced pressure to give a crude oily product, which was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 50:50) to afford methyl ester **16** as a yellow oil (16.4 g, 80%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.15–1.27 (m, 1 H, CH_2), 2.02–2.15 (m, 1 H, CH_2), 2.99 (s, 2 H, CH_2), 3.63 (s, 3 H, OCH_3), 3.72–3.87 (m, 7 H, 2 × OCH_2, OCH_3), 6.91 (d, *J* = 8.8 Hz, 2 H, ArH), 7.30 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.3 (CH_2), 45.6 (CH_2), 51.8 (OCH_3), 55.4 (OCH_3), 61.8 (2 × OCH_2), 107.5 (OCO), 113.4 (2 × CH), 127.1 (2 × CH), 133.8 (C), 159.1 (C), 169.0 (CO) ppm. $C_{14}H_{18}O_5$ (266.3): calcd. C 63.15, H 6.81; found C 63.19, H 6.91.

2-[2-(4-Methoxyphenyl)[1,3]dioxan-2-yl]ethanol (17): A solution of ester **16** (15 g, 56 mmol) in THF (40 mL) was slowly added to a suspension of $LiAlH_4$ (3.19 g, 84 mmol) in anhydrous THF (150 mL) at 0 °C under argon. The resulting mixture was stirred under reflux for 3 h. After cooling and addition of saturated aqueous NaOH (10%, 5 mL), CH_2Cl_2 (50 mL) was added and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (2 × 15 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under vacuum. The crude residue was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 50:50) to afford alcohol **17** as a colorless oil (11.3 g, 85%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25–1.32 (m, 1 H, CH_2), 1.96 (t, *J* = 5.3 Hz, 2 H, CH_2), 2.06–2.18 (m, 1 H, CH_2), 3.16 (br. s, 1 H, OH), 3.69–3.89 (m, 9 H, 3 × CH_2O, OCH_3), 6.93 (d, *J* = 8.8 Hz, 2 H, ArH), 7.38 (d, *J* = 8.8 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.5 (CH_2), 46.3 (CH_2), 55.3 (OCH_3), 58.6 (CH_2OH), 61.0 (2 × OCH_2), 103.1 (OCO), 114.1 (2 × CH), 128.4 (2 × CH), 131.5 (C), 159.3 (C) ppm. $C_{13}H_{18}O_4$ (238.3): calcd. C 63.53, H 7.61; found C 63.37, H 7.81.

[2-(4-Methoxyphenyl)[1,3]dioxan-2-yl]acetaldehyde (18): Pyridinium dichromate (PDC; 23.7 g, 63 mmol) was added portionwise to a solution of alcohol **17** (10 g, 42 mmol) in CH_2Cl_2 (200 mL). The reaction mixture was stirred at room temp. for 12 h, then diluted with Et_2O (100 mL) and filtered through a pad of Celite. Evaporation of the solvents delivered a crude oily product, which was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 45:55) to afford acetaldehyde derivative **18** as a yellowish oil (9.0 g, 91%). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.16–1.29 (m, 1 H, CH_2), 2.05–2.18 (m, 1 H, CH_2), 2.61 (d, *J* = 2.9 Hz, 2 H, CH_2CO), 3.83 (s, 3 H, OCH_3), 3.86–3.95 (m, 4 H, 2 × OCH_2), 6.94 (d, *J* = 8.9 Hz, 2 H, ArH), 7.36 (d, *J* = 8.9 Hz, 2 H, ArH), 9.95 (t, *J* = 2.9 Hz, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4 (CH_2), 55.3 (OCH_3), 56.9 (CH_2), 61.1 (2 × OCH_2), 100.4 (OCO), 114.3 (2 × CH), 128.3 (2 × CH), 130.8 (C), 159.5 (C), 201.3 (CHO) ppm. $C_{13}H_{16}O_4$ (236.3): calcd. C 66.09, H 6.83; found C 65.97, H 6.95.

[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]{2-[2-(4-methoxyphenyl)-[1,3]dioxan-2-yl]ethylidene}amine (19): SAMP (4.86 g, 37 mmol) and $MgSO_4$ (2 g) were added to a solution of the aldehyde **18** (8 g, 34 mmol) in CH_2Cl_2 (50 mL), and the mixture was stirred at room temp. for 12 h. After filtration and evaporation of the solvent under reduced pressure, the crude product was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 40:60) to afford **19** as a pale-yellow oil (11.4 g, 96%). $[a]_D^{25}$ = –66.6 (*c* = 1.30, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.18–1.29 (m, 1 H, CH_2), 1.71–1.93 (m, 4 H, 2 × CH_2), 2.02–2.13 (m, 1 H, CH_2), 2.62 (t, *J* = 5.7 Hz, 2 H, CH_2CN), 2.73–2.79 (m, 1 H, NCH_2), 3.36–3.55 [m, 7 H (1 H, NCH_2, OCH_3, NCH, OCH_2)], 3.78–3.91 (m, 7 H, OCH_3, 2 × OCH_2), 6.58 (t, *J* = 5.8 Hz, 1 H, CH=N), 6.93 (d, *J* = 8.9 Hz, 2 H, ArH), 7.33 (d, *J* = 8.9 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1 (CH_2), 25.6 (CH_2), 26.6 (CH_2), 48.2 (NCH_2), 50.3 (CH_2), 55.2 (OCH_3), 59.1 (OCH_3), 61.0 (2 × OCH_2), 63.0 (CH), 74.7 (OCH_2), 101.3 (OCO), 113.8 (2 × CH), 128.7 (2 × CH), 131.5 (C), 133.8 (C=N), 159.1 (C) ppm. $C_{19}H_{28}N_2O_4$ (348.5): calcd. C 65.49, H 8.10, N 8.04; found C 65.58, H 8.33, N 7.89.

***N*-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-*N*-{(1*R*)-1-[2-(4-methoxyphenyl)[1,3]dioxan-2-ylmethyl]but-3-enyl}acrylamide (20):** Obtained from **19** (1 g, 2.87 mmol) following the procedure reported for the synthesis of compound **5**. Purification by flash column chromatography on silica gel (ethyl acetate/hexanes, 20:80) furnished **20** as a yellow oil (829 mg, 65%). $[a]_D^{25}$ = –35.8 (*c* = 1.00, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.29 (m, 1 H, CH_2), 1.64–1.86 (m, 4 H, 2 × CH_2), 2.03–2.11 (m, 1 H, CH_2), 2.51–2.63 (m, 2 H, CH_2), 2.83–2.98 [m, 3 H (2 H, CH_2, 1 H, NCH_2)], 3.11–3.37 [m, 7 H (3 H, OCH_3, OCH_2, NCH, 1 H, NCH_2)], 3.66–3.78 [m, 8 H (3 H, OCH_3, 2 × OCH_2, NCH)], 4.92–5.03 (m, 2 H, CH_2=), 5.49 (dd, *J* = 2.2, 10.4 Hz, 1 H, CH_2=), 5.70–5.88 (m, 1 H, CH=), 6.22 (dd, *J* = 2.2, 17.2 Hz, 1 H, CH_2=), 6.91 (d, *J* = 8.6 Hz, 2 H, ArH), 7.03 (dd, *J* = 10.4, 17.2 Hz, 1 H, NCOCH=), 7.32 (d, *J* = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.2 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 38.0 (CH_2), 50.8 (CH_2), 51.6 (CH), 52.1 (CH_2), 55.3 (OCH_3), 57.5 (OCH_3), 58.8 (CH), 60.75 (OCH_2), 60.9 (OCH_2), 73.6 (OCH_2), 101.9 (OCO), 114.0 (2 × CH), 116.3 (CH_2=), 125.7 (CH_2=), 128.6 (2 × CH), 129.5 (CH=), 132.5 (C), 137.4 (CH=), 159.1 (C), 169.0 (CO) ppm. $C_{25}H_{36}N_2O_5$ (444.6): calcd. C 67.54, H 8.16, N 6.30; found C 67.79, H 8.03, N 6.29.

(6*R*)-1-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-6-[2-(4-methoxyphenyl)[1,3]dioxan-2-ylmethyl]-5,6-dihydro-1*H*-pyridin-2-one (21): Obtained by ring-closing metathesis of **20** (600 mg, 1.35 mmol) following the procedure reported for the synthesis of compound **10**.

Purification by column chromatography on silica gel (ethyl acetate/hexanes, 40:60) to afford **21** as a yellow oil (388 mg, 69%). $[\alpha]_D^{25}$ = –12.4 (c = 2.20, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22–1.29 (m, 1 H, CH_2), 1.32–1.43 (m, 1 H, CH_2), 1.53–1.65 (m, 1 H, CH_2), 1.83–2.19 [m, 5 H (4 H, 2 × CH_2, 1 H, CH_2)], 2.57–2.68 (m, 1 H, CH_2), 2.80 (ddd, J = 2.3, 6.0, 17.7 Hz, 1 H, CH_2), 2.93–3.02 (m, 1 H, NCH_2), 3.14–3.21 (m, 2 H, OCH_2), 3.26 (s, 3 H, OCH_3), 3.38–3.47 (m, 1 H, NCH_2), 3.62–3.71 (m, 1 H, NCH), 3.76–3.88 [m, 8 H (OCH_3, 2 × OCH_2, NCH)], 5.74 (dd, J = 2.5, 9.8 Hz, 1 H, CH=), 6.33–6.42 (m, 1 H, CH=), 6.91 (d, J = 8.7 Hz, 2 H, ArH), 7.28 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.2 (CH_2), 25.5 (CH_2), 27.6 (CH_2), 29.5 (CH_2), 45.5 (CH_2), 52.3 (CH_2), 55.3 (OCH_3, CH), 58.8 (OCH_3), 60.4 (CH), 60.8 (2 × OCH_2), 76.7 (OCH_2), 101.2 (OCO), 113.8 (2 × CH), 125.9 (CH=), 128.5 (2 × CH), 132.0 (C), 138.0 (CH=), 159.2 (C), 163.2 (CO) ppm. $C_{23}H_{32}N_2O_5$ (416.5): calcd. C 66.32, H 7.74, N 6.73; found C 66.48, H 7.94, N 6.81.

(6*R*)-1-[(2*S*)-2-(Methoxymethyl)pyrrolidin-1-yl]-6-[2-(4-methoxyphenyl)[1,3]dioxan-2-ylmethyl]piperidin-2-one (22): Obtained as previously described for the synthesis of **11**; catalytic hydrogenation of **21** (500 mg, 1.20 mmol) delivered **22** as a yellow oil (477 mg, 95%). $[\alpha]_D^{25}$ = –24.9 (c = 0.51, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.37–1.48 (m, 1 H, CH_2), 1.52–1.81 (m, 1 H, CH_2), 1.87–2.06 (m, 6 H, 3 × CH_2), 2.32 (t, J = 6.4 Hz, 2 H, CH_2), 2.40–2.64 (m, 4 H, 2 × CH_2), 3.05–3.12 (m, 1 H, NCH_2), 3.17–3.26 (m, 6 H, OCH_2, OCH_3, NCH), 3.45–3.54 [m, 2 H (1 H, NCH, 1 H, NCH_2)], 3.73–3.85 (m, 7 H, OCH_3, 2 × OCH_2), 6.82 (d, J = 8.6 Hz, 2 H, ArH), 7.11 (d, J = 8.6 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 17.4 (CH_2), 23.1 (CH_2), 27.2 (CH_2), 27.6 (CH_2), 31.3 (CH_2), 33.9 (CH_2), 34.6 (CH_2), 53.2 (CH_2), 55.3 (OCH_3), 58.7 (CH), 59.8 (OCH_3), 61.4 (CH), 62.3 (2 × OCH_2), 76.7 (OCH_2), 101.5 (OCO), 113.8 (2 × CH), 129.2 (2 × CH), 133.6 (C), 157.8 (C), 169.4 (CO) ppm. $C_{23}H_{34}N_2O_5$ (418.5): calcd. C 66.01, H 8.19, N 6.69; found C 66.24, H 7.92, N 6.80.

(1*RS*)-1-(4-Methoxyphenyl)-2-[(2*R*)-piperidin-2-yl]ethanol (4): Treatment of **22** (300 mg, 0.72 mmol) with BH_3·THF complex (as described previously for the conversion of **14** into **4**) afforded **4** as a mixture of (*RS*,*R*)-amino alcohols, which was used directly in the next step without further purification (135 mg, 80%).

2-(2-Bromo-4,5-dimethoxyphenyl)-1-{(2*R*)-2-[(2*RS*)-2-hydroxy-2-(4-methoxyphenyl)ethyl]piperidin-1-yl}ethanone (24): A solution of 2-bromo-4,5-dimethoxyphenylacetyl chloride (**23**; 622 mg, 2.12 mmol) in CH_2Cl_2 (5 mL) was added dropwise to a stirred ice-cooled mixture of amino alcohol **4** (250 mg, 1.06 mmol) and K_2CO_3 (292 mg, 2.12 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred at 0 °C for 6 h, then at room temp. for an additional 2 h. The mixture was filtered, and the filtrate was washed with water (15 mL), dried ($MgSO_4$) and concentrated. The oily residue was dissolved in a solution of K_2CO_3 (300 mg) in methanol/water (40 mL, 2:1, v/v), and the mixture was refluxed for 1 h. Concentration under reduced pressure delivered a brown oil, which was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with water (10 mL), aqueous NaOH (5%, 10 mL) then aqueous HCl (5%, 10 mL), dried ($MgSO_4$), and the solvent was evaporated under vacuum to give an oily residue. Purification by column chromatography on silica gel ($CHCl_3$) afforded **24** (1:1 mixture of two diastereoisomers) as a pale-yellow oil (464 mg, 89%). The isomeric ratio was evaluated from the ^1H NMR spectrum and integration of the C*H*OH protons: δ = 4.77 (dd, J = 6.0, 8.2 Hz, 1 H) and 4.91 (br. d, J = 8.7 Hz, 1 H) ppm.

2-(2-Bromo-4,5-dimethoxyphenyl)-1-{(2*R*)-2-[2-(4-methoxyphenyl)-2-oxoethyl]piperidin-1-yl}ethanone (3): PDC (275 mg, 0.73 mmol) and silica gel (2 g) were added to a solution of **24** (300 mg, 0.61 mmol) in CH_2Cl_2 (30 mL), and the mixture was stirred vigorously for 12 h. The reaction mixture was filtered through a pad of Celite, which was rinsed with CH_2Cl_2 (3 × 100 mL). Concentration of the filtrate under vacuum delivered the crude product, which was purified by flash column chromatography on silica gel (ethyl acetate/hexanes, 45:55) to afford **3** as a yellow oil (212 mg, 71%). $[\alpha]_D^{25}$ = –2.4 (c = 2.10, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$, 1:1 amide rotamers): δ = 1.35–1.71 (m, 6 H, 3 × CH_2), 2.66 (td, J = 2.4–13.5 Hz, 0.5 H), 3.08–3.37 (m, 2.5 H), 3.66–3.89 (m, 11.5 H), 4.63–?? (m, 0.5 H), 4.76 (m, 0.5 H), 5.30 (m, 0.5 H), 6.82 (m, 1 H, ArH), 6.91–7.03 (m, 3 H, ArH), 7.92 (d, J = 8.7 Hz, 1 H, ArH), 8.04 (d, J = 8.8 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$, 1:1 amide rotamers): δ = 18.7 (CH_2), 19.3 (CH_2), 25.5 (CH_2), 25.6 (CH_2), 27.3 (CH_2), 29.3 (CH_2), 37.6 (CH_2), 38.5 (CH_2), 38.9 (CH_2), 40.5 (CH_2), 40.9 (CH_2), 42.0 (CH_2), 46.6 (NCH), 49.6 (NCH), 55.5 (OCH_3), 55.55 (OCH_3), 56.0 (OCH_3), 56.05 (2 × OCH_3), 56.1 (OCH_3), 112.8 (CH), 113.2 (CH), 113.8 (2 × CH), 113.9 (2 × CH), 114.3 (C), 114.6 (C), 115.3 (2 × CH), 127.1 (C), 127.5 (C), 129.6 (C), 129.8 (C), 130.3 (2 × CH), 130.8 (2 × CH), 130.9 (C), 130.95 (C), 148.3 (C), 148.4 (C), 163.6 (C), 163.8 (C), 169.2 (NCO), 169.5 (NCO), 195.8 (CO), 196.8 (CO) ppm. $C_{24}H_{28}BrNO_5$ (490.4): calcd. C 58.78, H 5.76, N 2.86; found C 58.57, H 5.69, N 2.81.

(9a*R*)-3-(2-Bromo-4,5-dimethoxyphenyl)-2-(4-methoxyphenyl)-1,6,7,8,9,9a-hexahydroquinolizin-4-one (2): A solution of **3** (250 mg, 0.51 mmol) in 5% ethanolic KOH (10 mL) was refluxed for 1 h. The reaction mixture was then concentrated under reduced pressure, diluted with water (15 mL) and extracted with CH_2Cl_2 (3 × 30 mL). The combined organic layers were washed with water (10 mL) and HCl (5%, 10 mL) and dried ($MgSO_4$). After evaporation of the solvent under vacuum, purification of the residue by column chromatography on silica gel (ethyl acetate/hexanes, 40:60) afforded **2** as a pale-yellow oil (155 mg, 69%). $[\alpha]_D^{25}$ = –37.3 (c = 0.50, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.36–1.95 (m, 6 H, 3 × CH_2), 2.61–2.82 [m, 3 H (1 H, NCH_2, 2 H, CH_2)], 3.64 (s, 3 H, OCH_3), 3.65–3.71 (m, 1 H, NCH), 3.75 (s, 3 H, OCH_3), 3.85 (s, 3 H, OCH_3), 4.56 (br. d, 1 H, NCH_2), 6.45 (s, 1 H, ArH), 6.69 (d, J = 8.7 Hz, 2 H, ArH), 7.00 (s, 1 H, ArH), 7.02 (d, J = 8.7 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.3 (CH_2), 24.6 (CH_2), 33.4 (CH_2), 37.6 (CH_2), 42.8 (NCH_2), 53.4 (NCH), 55.2 (OCH_3), 55.9 (OCH_3), 56.0 (OCH_3), 113.4 (2 × CH), 114.7 (C), 114.9 (CH), 115.5 (CH), 128.9 (2 × CH), 130.4 (C), 130.6 (C), 131.5 (C), 145.7 (C), 148.0 (C), 148.6 (C), 159.1 (C), 166.2 (CO) ppm. $C_{24}H_{26}BrNO_4$ (472.4): calcd. C 61.02, H 5.55, N 2.97; found C 60.89, H 5.42, N 2.71.

(9a*R*)-2,3,6-Trimethoxy-9,9a,10,11,12,13-hexahydro-13a-azabenzo[*b*]triphenylen-14-one (25): A solution of **2** (100 mg, 0.21 mmol), AIBN (5 mg) and Bu_3SnH (120 mg, 0.11 mL, 0.42 mmol) in freshly distilled benzene (40 mL) was refluxed under argon for 3 h. After cooling, the reaction mixture was concentrated under vacuum, and the resulting mixture was purified by column chromatography on silica gel (ethyl acetate/hexanes, 40:60) to afford **25** as a colorless solid (75 mg, 91%); m.p. 199–200 °C. $[\alpha]_D^{25}$ = –102.3 (c = 0.53, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 1.41–1.68 (m, 4 H, 2 × CH_2), 1.87–2.09 (m, 2 H, CH_2), 2.91 (td, J = 3.1, 13.0 Hz, 1 H, CH_2), 3.04 (dd, J = 11.0, 16.2 Hz, 1 H, NCH_2), 3.43 (dd, J = 4.8, 16.2 Hz, 1 H, NCH_2), 3.54–3.62 (m, 1 H, NCH), 4.06 (s, 3 H, OCH_3), 4.11 (s, 3 H, OCH_3), 4.13 (s, 3 H, OCH_3), 4.72 (br. d, J = 13.0 Hz, 1 H, CH_2), 7.22 (dd, J = 2.4, 9.4 Hz, 1 H, ArH), 7.36 (s, 1 H, ArH), 7.84 (d, J = 2.4 Hz, 1 H, ArH), 8.05 (d, J = 9.4 Hz, 1 H, ArH), 9.41 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.9 (CH_2), 24.7 (CH_2), 32.7 (CH_2), 32.9 (CH_2), 42.8 (CH_2), 52.8 (CH), 55.5 (OCH_3), 55.7 (OCH_3), 55.9 (OCH_3), 102.9 (CH), 104.4

(CH), 108.7 (C), 115.5 (CH), 123.5 (C), 124.1 (CH), 125.5 (C), 126.6 (CH), 126.8 (C), 127.3 (C), 130.1 (C), 148.4 (C), 149.3 (C), 157.3 (C), 167.3 (CO) ppm. $C_{24}H_{25}NO_4$ (391.5): calcd. C 73.64, H 6.44, N 3.58; found C 73.79, H 6.42, N 3.86.

(*R*)-Boehmeriasin A (1d): A solution of **25** (70 mg, 0.18 mmol) in THF (2 mL) was added dropwise to an ice-cooled, stirred suspension of $LiAlH_4$ (10 mg, 0.27 mmol) in dry THF (3 mL). The reaction mixture was refluxed under argon for 3 h, then cooled to 0 °C and carefully quenched by addition of an aqueous NaOH solution (10%, 2 mL); CH_2Cl_2 (5 mL) was added, and the organic layer was separated. The aqueous layer was extracted with CH_2Cl_2 (3×5 mL), and the combined organic layers were dried ($MgSO_4$), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography on silica gel ($CHCl_3/CH_3OH$, 95:5) to yield boehmeriasin A (**1d**) as a colorless solid (51 mg, 75%); m.p. 215–217 °C (ref.[9] 216–218 °C). $[a]_D^{25}$ = –80.2 (c = 0.15, CH_3OH) {ref.[9] $[a]_D^{25}$ = –80.4 (c = 0.1, CH_3OH)}. Analytical and spectroscopic data were in agreement with those reported for the natural product.[9]

Acknowledgments

We are grateful to the Centre National de la Recherche Scientifique (CNRS) and the Région Nord-Pas-de-Calais for financial support (grant to D. D.). This work was also supported by the Programme PRIM (Région Nord-Pas-de-Calais).

[1] A. N. Ratnagiriswaran, K. Venkatachalam, *Ind. J. Chem. Res.* **1935**, *22*, 433–441.

[2] a) Z. Li, Z. Jin, R. Huang, *Synthesis* **2001**, 2365–2378; b) E. Gellert, *J. Nat. Prod.* **1982**, *45*, 50–73; c) I. R. C. Bick, W. Sinchai, in *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1981**, vol. 19, pp. 193–220; d) T. R. Govindachari, N. Viswanathan, *Heterocycles* **1978**, *11*, 587–613; e) M. Suffness, G. A. Cordell, in *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1985**, vol. 25, pp. 156–163; f) M. Suffness, G. A. Cordell, in *The Alkaloids* (Ed.: A. Brossi), Academic Press, New York, **1985**, vol. 25, pp. 3–355.

[3] For a recent review, see: a) W. Gao, A. P.-C. Chen, C.-H. Leung, E. A. Gullen, A. Fürstner, Q. Shi, L. Wei, K.-H. Lee, Y.-C. Cheng, *Bioorg. Med. Chem. Lett.* **2008**, *18*, 704–709; b) W. Gao, S. Bussom, S. P. Grill, E. A. Gullen, Y.-C. Hu, X. Huang, S. Zhong, C. Kaczmarek, J. Gutierrez, S. Francis, D. C. Baker, S. Yu, Y.-C. Cheng, *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4338–4342; c) L. Wei, A. Brossi, R. Kendall, K. F. Bastow, S. L. Morris-Natschke, Q. Shi, K.-H. Lee, *Bioorg. Med. Chem.* **2006**, *14*, 6560–6569; d) J. P. Michael, *Nat. Prod. Rep.* **2007**, *24*, 191–222; e) J. P. Michael, *Nat. Prod. Rep.* **2004**, *21*, 625–649; f) J. P. Michael, *Nat. Prod. Rep.* **2003**, *20*, 458–475; g) S. K. Lee, K.-A. Nam, Y.-H. Hea, *Planta Med.* **2003**, *69*, 21–25; h) J. P. Michael, *Nat. Prod. Rep.* **2002**, *19*, 719–741; i) J. P. Michael, *Nat. Prod. Rep.* **2001**, *18*, 520–542.

[4] a) M. G. Banwell, A. Bezos, C. Burns, I. Kruszelnicki, C. R. Parish, S. Su, M. O. Sydnes, *Bioorg. Med. Chem. Lett.* **2006**, *16*, 181–185 and references cited therein; b) L. Wei, Q. Shi, K. F. Bastow, A. Brossi, S. L. Morris-Natschke, K. Nakagawa-Goto, T.-S. Wu, S.-L. Pan, C.-M. Teng, K.-H. Lee, *J. Med. Chem.* **2007**, *50*, 3674–3680.

[5] For representative recent examples, see: a) M. Cui, Q. Wang, *Eur. J. Org. Chem.* **2009**, 5445–5451; b) S. Yamashita, N. Kurono, H. Senboku, M. Tokuda, K. Orito, *Eur. J. Org. Chem.* **2009**, 1173–1180; c) S. Kim, Y. M. Lee, J. Lee, T. Lee, Y. Fu, Y. Song, J. Cho, D. Kim, *J. Org. Chem.* **2007**, *72*, 4886–4891; d) A. Fürstner, J. W. J. Kennedy, *Chem. Eur. J.* **2006**, *12*, 7398–7410; e) S. Kim, T. Lee, E. Lee, J. Lee, G.-j. Fan, S. K. Lee, D. Kim, *J. Org. Chem.* **2004**, *69*, 3144–3149; f) S. Lebrun, A. Couture, E. Deniau, P. Grandclaudon, *Tetrahedron* **1999**, *55*, 2659–2670; g) H. Suzuki, S. Aoyagi, C. Kibayashi, *J. Org. Chem.* **1995**, *60*, 6114–6122; h) H. Suzuki, S. Aoyagi, C. Kibayashi, *Tetrahedron Lett.* **1995**, *36*, 935–936.

[6] I. S. de la Lande, *Aust. J. Exp. Biol. Med. Sci.* **1948**, *26*, 181–187.

[7] S. R. Johns, J. A. Lamberton, A. A. Sioumis, R. I. Willing, *Aust. J. Chem.* **1970**, *23*, 353–361.

[8] X. F. Cai, X. J. Jin, D. Lee, Y. T. Yang, K. Lee, Y.-S. Hong, J.-H. Lee, J. J. Lee, *J. Nat. Prod.* **2006**, *69*, 1095–1097.

[9] a) Y. Luo, Y. Liu, D. Luo, X. Gao, B. Li, G. Zhang, *Planta Med.* **2003**, *69*, 842–845; b) Y. Luo, X. Gao, Y. Liu, Y. Tian, J. Gu, M. Zhou, B. Li, G. Zhang, CN 1463973, **2003** (*Chem. Abstr.* **2005**, *142*, 385974).

[10] J. Yan, D. Luo, Y. Luo, X. Gao, G. Zhang, *Int. J. Gynecol. Cancer* **2006**, *16*, 165–170.

[11] a) A. Job, C. F. Janeck, W. Bettray, R. Peters, D. Enders, *Tetrahedron* **2002**, *58*, 2253–2329; b) S. Lebrun, A. Couture, E. Deniau, P. Grandclaudon, *Org. Lett.* **2007**, *9*, 2473–2476; c) D. Dumoulin, S. Lebrun, E. Deniau, A. Couture, P. Grandclaudon, *Eur. J. Org. Chem.* **2009**, 3741–3752.

[12] For reviews, see: a) T. J. Donohoe, A. J. Orr, M. Bingham, *Angew. Chem. Int. Ed.* **2006**, *45*, 2664–2670; b) A. Dieters, S. F. Martin, *Chem. Rev.* **2004**, *104*, 2199–2238; c) R. H. Grubbs, in *Handbook of Metathesis*, Wiley-VCH, Weinheim, **2003**, vol. 1–3.

[13] D. S. Bhakuni, P. K. Gupta, *Indian J. Chem.* **1982**, *21B*, 393–395.

[14] For radical cyclization, see ref.[5g,5h] and T. Takeuchi, A. Ishita, J.-i. Matsuo, H. Ishibashi, *Tetrahedron* **2007**, *63*, 11101–11107.

[15] A. P. Kozikowski, P. D. Stein, *J. Org. Chem.* **1984**, *49*, 2301–2309.

[16] D. Enders, J. Gries, Z.-S. Kim, *Eur. J. Org. Chem.* **2004**, 4471–4482.

[17] T. E. Young, M. F. Mizianty, *J. Med. Chem.* **1966**, *9*, 635–637.

Received: December 3, 2009
Published Online: February 16, 2010

