Synthesis of Both Enantiomers of the *Streptomyces* Alkaloid 4-*epi*-SS20846A

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Abstract: The enantiodivergent synthesis of the *Streptomyces* alkaloid 4-*epi*-SS20846A was based on a Takai olefination/Suzuki–Miyaura coupling sequence for the highly stereoselective introduction of the *E*,*E*-pentadienyl side chain on the piperidine skeleton. Optical separation of a key hydroxylated enamide ester, prepared by palladium-catalyzed methoxycarbonylation of a lactam-derived enol phosphate, was successfully achieved by both lipase-catalyzed kinetic resolution and semipreparative HPLC. This approach allowed us to obtain the enantiopure target alkaloid in 35–38% yield over six steps.

Key words: alkaloids, lactams, carbonylation, olefination, cross-coupling

Chemical screening for secondary metabolites in the culture broth of *Streptomyces luteogriseus* (strain FH-S 1307) has led to the discovery of two major 4-hydroxypiperidine alkaloids bearing a 1,3-pentadienyl moiety (compounds **1** and **2**, Figure 1), which are thought to be intermediates in the biosynthesis of the well-known antibiotic streptazoline (**3**, isolated from the same broth as a minor secondary metabolite).[1] Of these alkaloids, only the *trans*-compound **2**, which is named SS20846A as it was first isolated from *Streptomyces* sp. S20846,[2] has attracted attention from synthetic chemists due to its interesting antibacterial and anticonvulsant properties,[3] whereas to the best of our knowledge only two syntheses focused on its *cis*-epimer **1** have been reported so far.[4]

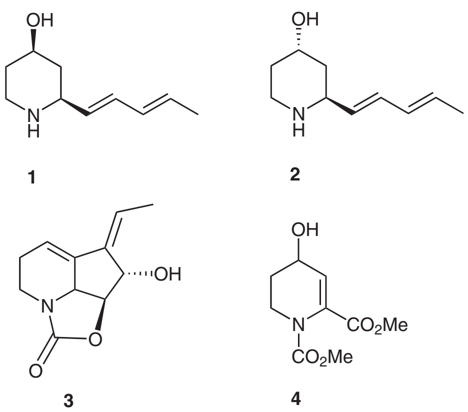

Figure 1

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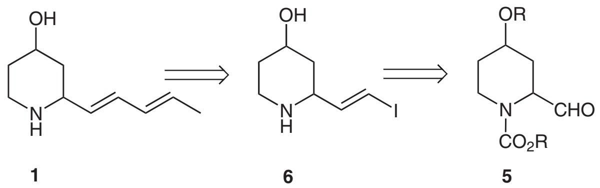
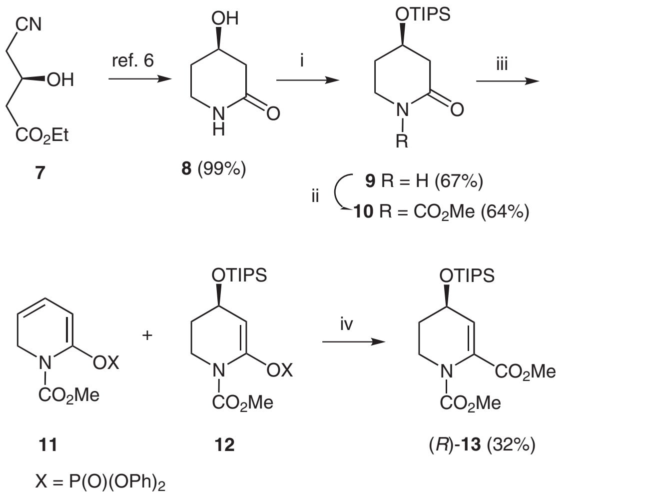
We have recently shown that the 4-hydroxypyridine derivative **4** (Figure 1) is a useful intermediate in the synthesis of 4-hydroxypiperidine alkaloids. By elaboration of the ester functionality and enamide double bond, it was possible to synthesize the glycosidase inhibitor fagomine and all stereoisomers of 4-hydroxypipecolic acid.[5a,b] Given the scarce attention received by 4-*epi*-SS20846A, and because the availability of synthetic material could be useful for biological studies on this natural alkaloid, we therefore decided to further exploit the potential of chiral intermediate **4** for the synthesis of both enantiomers of **1**.

A retrosynthetic analysis is shown in Scheme 1. The *cis*- and *trans*-aldehydes **5** are key intermediates which have already been employed for the synthesis of both **1** and **2**;[3e,4b] however, for such a purpose, Wittig olefinations were carried out, which resulted in the predominant formation of the 1*Z*,3*E*- over the 1*E*,3*E*-isomer. This required an olefin isomerization by exposure to iodine and a difficult chromatographic separation of the desired isomer from the residual 1*Z*,3*E*-compound.[3e] To avoid this problem, we planned a stereoselective Takai olefination of *cis*-**5** to give iodoalkene **6**, followed by a Suzuki–Miyaura reaction with an MIDA boronate, a sequence which should provide the *E*,*E*-isomer only.



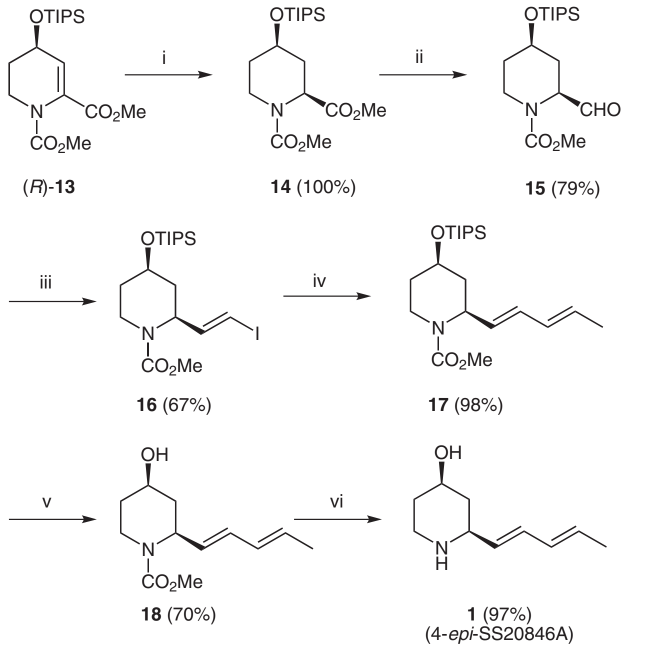
Scheme 1 Retrosynthetic analysis

We first tried the synthesis of enantiopure intermediate **4** (Scheme 2) starting from commercially available nitrile **7** (96% ee) which was converted into 4-hydroxy-δ-valerolactam (**8**, 99%) by hydrogenation in methanol over PtO_2 as reported.[6] After sequential protection under standard conditions as the TIPS ether **9** (67%) and then the *N*-CO_2Me carbamate **10** (64%), the latter was converted into the corresponding enol phosphate **12** by treatment with potassium hexamethyldisilazide in tetrahydrofuran at –78 °C followed by diphenyl chlorophosphate.[7] Unfortunately, this resulted in the formation of the elimination product **11** in a 1:1 ratio with **12**, in analogy with our previous findings when trying to prepare the enol triflates from other similar 4-silyloxy ethers.[8,9] This mixture was not separated but directly subjected to palladium-catalyzed methoxycarbonylation[7] to give ester (*R*)-**13** in low yield (32%) after chromatography. In order to obtain enantiopure alcohol **4** in synthetically useful amounts, we therefore resorted to the optical separation of the racemic compound by a lipase-catalyzed kinetic resolution which we have previously reported and which provided (+)-**4** and (–)-**4** with ee higher than 99.5%.[10,11]



Scheme 2 *Reagents and conditions*: i. TIPSCl, imidazole, DMF, 40 °C, 8 h; ii. $ClCO_2Me$, *n*-BuLi, THF, –78 °C, 0.5 h; iii. KHMDS, THF, –78 °C, 1.5 h; then $(PhO)_2P(O)Cl$, –78 °C, 1 h; iv. $Pd(OAc)_2$, Ph_3P, MeOH, CO (1 atm), Et_3N, DMF, 75 °C, 2 h.

With a sufficient amount of the enantiopure starting material (*R*)-**4** (and its enantiomer) we proceeded with the synthesis of compound **1** as outlined in Scheme 3. After protection of the hydroxy group of (*R*)-**4** as the TIPS ether (91%),[5b,c] compound (*R*)-**13** was subjected to heterogeneous hydrogenation to quantitatively give the diastereopure *cis*-pipecolic acid methyl ester derivative **14**.[5b,c] Reduction to aldehyde **15** (79%) by diisobutylaluminum hydride in dichloromethane at –78 °C set the stage for the Takai olefination. Although we found that no epimerization occurred at the C2 stereocenter of **15**, we preferred to use this aldehyde for the next step immediately after chromatography. The Takai olefination[12] proceeded smoothly and, despite the formation of minor amounts of the *Z*-isomer reported in some cases,[13] it provided iodoalkene **16** in 67% yield as the *E*-stereoisomer only. In fact, only the signals of this isomer were present in the ^1H NMR spectrum of the crude reaction mixture, with a coupling constant value of 14.4 Hz for the olefinic protons, consistent with the *E* geometry. The olefination was then followed by the palladium(0)-catalyzed coupling with *trans*-1-propenylboronic acid MIDA (methyliminodiacetic acid) ester,[14] which was carried out in tetrahydrofuran in the presence of either an aqueous sodium hydroxide solution (98%)[15] or with aqueous potassium phosphate as a base (55%).[16] In both cases, the reaction provided olefin **17** as the 1*E*,3*E*-stereoisomer, although in a 3.8:1 mixture with a minor isomer which turned out to be, unexpectedly, the 1*E*,3*Z*-isomer. This was not due to poor stereoselectivity of the Suzuki–Miyaura coupling, but to the presence of the *cis*-isomer (about 21%) in the commercial MIDA boronate we used for the coupling.[17] The cross-coupling product mixture was difficult to separate by standard chromatography but, after removal of the TIPS protection with tetrabutylammonium fluoride in tetrahydrofuran to give **18** (97%),[18] purification of the latter was possible by silver ion chromatography, a chromatographic technique which is normally used for the separation of fatty acid derivatives on the basis of the number, position and geometry of the double bonds.[19] This allowed us to separate the 1*E*,3*E*-isomer (70% yield) from the 1*E*,3*Z*-isomer. After removal of the *N*-CO_2Me group from **18** by potassium hydroxide in refluxing aqueous methanol, alkaloid **1** (35% yield over six steps) was obtained after chromatography on silica gel as a white solid, with spectroscopic and analytical data identical to those reported in the literature for the synthetic material,[4] including the optical rotation whose measured value was significantly higher than that reported for the natural compound {$[\alpha]_D^{20}$ –13.0 (*c* 1.0, $CHCl_3$)}.[1] Using the same approach, unnatural (+)-4-*epi*-SS20846A [(+)-**1**] {$[\alpha]_D^{25}$ +36.3 (*c* 0.41, $CHCl_3$)} was prepared in 38% overall yield from (*S*)-**4**.



Scheme 3 *Reagents and conditions*: i. H_2, 10% Pd/C, $NaHCO_3$, EtOAc, r.t., 47 h; ii. DIBAL-H, CH_2Cl_2, –78 °C, 4 h; iii. CHI_3, $CrCl_2$, THF, 0 °C → r.t., 16 h; iv. *trans*-1-propenylboronic acid MIDA ester, $Pd(OAc)_2$, SPhos, 1 M NaOH, THF, 50 °C, 5.5 h; v. TBAF, THF, r.t., 8.5 h; vi. KOH, MeOH–H_2O (4:1), reflux, 5 d.

In conclusion, we have demonstrated the usefulness of alcohol **4** in the synthesis of 4-hydroxypiperidine alkaloids by preparing the natural alkaloid 4-*epi*-SS20846A and its enantiomer in a few steps and good overall yield. As the Takai olefination gave exclusively the *E*-isomer, our sequence, which includes the Suzuki–Miyaura coupling of an MIDA boronate, proved better than the Wittig olefination approach for the introduction of the *E*,*E*-diene moiety and can therefore be extended to the synthesis of closely related compounds. Stereoselectivity was limited only by the isomeric purity of the commercial boronate ester used in the Suzuki reaction but silver ion chromatography was effective in the separation of the *E*,*E*- from the unwanted *E*,*Z*-isomer, a technique that can find application in similar instances.

Standard chromatographic separations were performed under pressure on silica gel 60 (Merck, 70–230 mesh) using flash-column techniques; R_f values refer to TLC carried out on 0.25-mm silica gel plates with the same eluent indicated for the column chromatography. THF and toluene were distilled from Na/benzophenone. CH_2Cl_2 and *n*-hexane were distilled from CaH_2. Commercial anhyd DMF and MeOH were used. ^1H NMR (400 and 200 MHz) and ^{13}C NMR (100.4 and 50.33 MHz) spectra were recorded at 25 °C. Mass spectroscopic analyses were carried out either by direct inlet on an LCQ Fleet Ion Trap LC/MS system (Thermo Fisher Scientific) with an electrospray ionization (ESI) interface in the positive mode or by EI at 70 eV. Compound **8**[6] is known, and **13**, **14** were prepared as reported for their enantiomers.[5b,c] The lipase-catalyzed kinetic resolution of **4** was carried out as reported.[5b]

Preparation of the Silica Gel for Silver Ion Chromatography

A 1 M aq soln of $AgNO_3$ (12 mL) was prepared in a 100-mL beaker wrapped in aluminum foil; silica gel (20 g) was added and mixed with a glass spatula. The beaker was placed in an oven at 150 °C for 1 h; the silica gel was gently mixed after 30 min. The beaker was then covered with riddled aluminum foil and placed in a desiccator under reduced pressure. Drying was continued until a constant weight was reached (2.5 h). The silica gel was stored in the dark.

Preparation of the TLC Plates for Silver Ion Chromatography

TLC plates (2.5 × 8 cm) were completely eluted (15 min) in a development chamber wrapped in aluminum foil, with a 1 M aq soln of $AgNO_3$ (5 mL). The plates were then dried in an oven at 100 °C for 15 min and stored in the dark. Compounds were revealed by *p*-anisaldehyde stain.

(4*R*)-4-(Triisopropylsilyloxy)piperidin-2-one (9)

Imidazole (306 mg, 4.5 mmol) and TIPSCl (0.64 mL, 3.0 mmol) were added to a soln of lactam **8** (173 mg, 1.5 mmol) in anhyd DMF (4.5 mL) and the mixture was heated at 40 °C. After 7 h, a further amount of TIPSCl (0.11 mL, 0.5 mmol) was added and the reaction was left at 40 °C until completion (TLC). The mixture was cooled to r.t., H_2O (25 mL) was added and the product was extracted with Et_2O (5 × 20 mL); the combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated to give crude **9**. Purification by flash chromatography [*n*-hexane, then *n*-hexane–EtOAc, 1:2; R_f = 0.26] gave pure **9** as a colorless oil; yield: 274 mg (67%).

$[\alpha]_D^{26}$ –1.5 (*c* 0.88, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 5.89 (br s, NH), 4.32–4.27 (m, 1 H), 3.69–3.52 (m, 1 H), 3.26–3.19 (m, 1 H), 2.58 (dd, *J* = 17.4, 4.5 Hz, 1 H), 2.42 (ddd, *J* = 17.4, 5.1, 0.9 Hz, 1 H), 1.93–1.82 (m, 2 H), 1.07–1.04 (m, 21 H).

^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 171.1 (s), 65.1 (d), 41.2 (t), 37.9 (t), 30.5 (t), 18.0 (q, 6 C), 12.2 (d, 3 C).

ESI-MS: *m*/*z* (%) = 565 (100) [2 M^+ + Na], 543 (42) [2 M^+ + 1], 272 (6) [M^+ + 1].

Anal. Calcd for $C_{14}H_{29}NO_2Si$: C, 61.94; H, 10.77; N, 5.40. Found: C, 61.60; H, 10.57; N, 5.40.

Methyl (4*R*)-2-Oxo-4-(triisopropylsilyloxy)piperidine-1-carboxylate (10)

A soln of lactam **9** (260 mg, 0.96 mmol) in anhyd THF (10 mL), under stirring and nitrogen atmosphere, was cooled to –78 °C and 1.6 M *n*-BuLi in hexanes (0.6 mL, 1 equiv) was added dropwise, keeping the temperature below –70 °C during the addition. The mixture was stirred at –78 °C for 15 min and methyl chloroformate (0.082 mL, 1.1 equiv) was then added dropwise, keeping the temperature constant. After 10 min, the cold alcohol bath was removed and the solution was allowed to warm to 0 °C (10 min). The reaction was quenched by the addition of sat. aq $NaHCO_3$ (6 mL) and the mixture was extracted with CH_2Cl_2 (3 × 6 mL). The combined organic extracts were dried over Na_2SO_4, filtered and the solvent was evaporated to give crude **10**. Purification by flash chromatography (*n*-hexane–EtOAc, 5:2; R_f = 0.29) afforded pure compound **10** as a colorless oil; yield: 203 mg (64%).

$[\alpha]_D^{23}$ +5.9 (*c* 0.97, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$): δ = 4.33–4.29 (m, 1 H), 3.91 (ddd, *J* = 14.1, 9.4, 4.9 Hz, 1 H), 3.86 (s, 3 H), 3.72 (dt, *J* = 12.9, 5.5 Hz, 1 H), 2.72 (ddd, *J* = 17.0, 4.5, 0.8 Hz, 1 H), 2.61 (ddd, *J* = 17.0, 4.9, 1.6 Hz, 1 H), 2.16–1.88 (m, 2 H), 1.06–1.03 (m, 21 H).

^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 169.6 (s), 154.9 (s), 64.9 (d), 53.9 (q), 44.5 (t), 42.1 (t), 31.4 (t), 17.9 (q, 6 C), 12.1 (d, 3 C).

ESI-MS: *m*/*z* (%) = 681 (100) [2 M^+ + Na], 330 (25) [M^+ + 1].

Anal. Calcd for $C_{16}H_{31}NO_4Si$: C, 58.32; H, 9.48; N, 4.25. Found: C, 58.32; H, 9.10; N, 3.94.

Methyl (2*S*,4*R*)-2-Formyl-4-(triisopropylsilyloxy)piperidine-1-carboxylate (15)

A soln of ester **14** (374 mg, 1.0 mmol) in anhyd CH_2Cl_2 (14 mL) was cooled to –78 °C and 1 M DIBAL-H in hexane (1.2 mL, 1.2 mmol) was added dropwise, keeping the temperature below –75 °C. The mixture was left at –78 °C under stirring and, after 2 h, a further amount of 1 M DIBAL-H was added (0.6 mL, 0.6 mmol). After an additional 2 h, the reaction was quenched by adding anhyd MeOH (1.2 mL) at –78 °C. Then, after 5 min, the cold bath was removed and sat. aq NH_4Cl (30 mL) was added. The mixture was diluted with CH_2Cl_2 (20 mL) and the product was extracted with CH_2Cl_2 (3 × 20 mL); the combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated to obtain crude **15**. Purification by flash chromatography (*n*-hexane–EtOAc, 4:1; R_f = 0.18) afforded pure aldehyde **15** as a colorless oil; yield: 270 mg (79%). This was immediately used for the next step.

$[\alpha]_D^{25}$ –31.2 (*c* 0.28, $CHCl_3$).

^1H NMR (400 MHz, $CDCl_3$; 1.3:1 mixture of rotamers): δ = 9.60 (s, 1 H), 4.66 (br d, *J* = 6.4 Hz, 1 H, major), 4.47 (br d, *J* = 6.6 Hz, 1 H, minor), 4.25 (br s, 1 H), 4.01 (br d, *J* = 11.7 Hz, 1 H, minor), 3.85 (br d, *J* = 12.7 Hz, 1 H, major), 3.74 (s, 3 H, major), 3.68 (s, 3 H, minor), 3.41–3.30 (m, 1 H), 2.41–2.32 (m, 1 H), 1.97–1.91 (m, 1 H), 1.69–1.56 (m, 2 H), 1.04 (s, 21 H); unless specified, signals refer to both rotamers.

ESI-MS: *m*/*z* (%) = 343 (2) [M^+], 314 (29), 300 (43), 146 (51), 138 (100).

Methyl (2*S*,4*R*)-2-[(*E*)-2-Iodovinyl]-4-(triisopropylsilyloxy)piperidine-1-carboxylate (16)

A soln of aldehyde **15** (270 mg, 0.79 mmol) and CHI_3 (590 mg, 1.50 mmol) in anhyd THF (4 mL) was added dropwise to a green suspension of $CrCl_2$ (553 mg, 4.50 mmol) in anhyd THF (11 mL) cooled at 0 °C (ice bath). The green color turned dark red to brown in a few minutes. After 5 min, the ice bath was removed and the mixture was stirred at r.t. for 16 h. Water and ice were added (45 mL) and the mixture was extracted with Et_2O (6 × 30 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated to obtain crude **16**. Purification by flash chromatography [*n*-hexane, then *n*-hexane–EtOAc, 12:1; R_f = 0.19] gave pure **16** as a colorless oil; yield: 247 mg (67%).

$[\alpha]_D^{22}$ –58.7 (*c* 0.84, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.01 (dd, *J* = 14.4, 7.6 Hz, 1 H), 6.16 (d, *J* = 14.4 Hz, 1 H), 4.75–4.68 (br m, 1 H), 4.24–4.21 (m, 1 H), 3.89 (br d, *J* = 12.7 Hz, 1 H), 3.69 (s, 3 H), 3.33 (td, *J* = 12.9, 2.9 Hz, 1 H), 1.88–1.78 (m, 2 H), 1.73–1.58 (m, 2 H), 1.08 (s, 21 H).

^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 156.0 (s), 145.7 (d), 76.5 (d), 64.5 (d), 54.2 (q), 52.7 (d), 36.7 (t), 34.6 (t), 32.7 (t), 18.2 (q, 3 C), 18.1 (q, 3 C), 12.2 (d, 3 C).

ESI-MS: *m*/*z* (%) = 467 (5) [M$^+$], 424 (55), 340 (32), 214 (41), 145 (100).

Anal. Calcd for $C_{18}H_{34}INO_3Si$: C, 46.25; H, 7.33; N, 3.00. Found: C, 46.11; H, 7.24; N, 2.87.

Methyl (2*S*,4*R*)-2-(Penta-1,3-dienyl)-4-(triisopropylsilyloxy)piperidine-1-carboxylate (17)

A soln of the Pd/SPhos catalyst was prepared by mixing $Pd(OAc)_2$ (5.90 mg, 0.026 mmol) and SPhos (21.6 mg, 0.052 mmol) in anhyd toluene (1.5 mL). The resulting solution was stirred at r.t. for 45 min and used in the Suzuki reaction, as follows. Vinyl iodide **16** (247 mg, 0.53 mmol) and *trans*-1-propenylboronic acid MIDA ester (197 mg, 1.0 mmol) were dissolved in anhyd THF (30 mL) and the catalyst soln (1.5 mL, 0.026 mmol Pd, 5% mol Pd) was added dropwise, followed by degassed 1 M NaOH (5 mL), under vigorous stirring. The mixture was heated at 50 °C for 5.5 h, then cooled to r.t. EtOAc (70 mL) was added and the organic phase was washed once with H_2O (30 mL), dried over Na_2SO_4 and filtered, and the solvent was evaporated to obtain crude **17**. Purification by flash chromatography (*n*-hexane–EtOAc, 12:1; R_f = 0.15) gave compound **17** as a 4:1 mixture of the *E*,*E*- and *E*,*Z*-isomers as a colorless oil; yield: 198 mg (98%).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.33 (dd, *J* = 15.2, 10.9 Hz, 1 H, *E*,*Z*), 6.13 (dd, *J* = 15.2, 7.4 Hz, 1 H, *E*,*Z*), 6.02–5.93 (m, 3 H, *E*,*E* and 1 H, *E*,*Z*), 5.66–5.58 (m, 1 H, *E*,*E*), 5.45–5.40 (m, 1 H, *E*,*Z*), 4.83–4.76 (m, 1 H, *E*,*Z*), 4.76–4.69 (m, 1 H, *E*,*E*), 4.24–4.21 (m, 1 H), 3.93–3.82 (m, 1 H), 3.70 (s, 3 H, *E*,*Z*), 3.68 (s, 3 H, *E*,*E*), 3.42–3.32 (m, 1 H), 1.88–1.81 (m, 2 H), 1.73 (d, *J* = 6.6 Hz, 3 H, *E*,*E*), 1.72 (d, *J* = 7.0 Hz, 3 H, *E*,*Z*), 1.69–1.66 (m, 2 H, *E*,*E*), 1.65–1.63 (m, 2 H, *E*,*Z*), 1.06 (s, 21 H, *E*,*E*), 1.05 (s, 21 H, *E*,*Z*).

^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 156.1 (s), 133.6 (d, *E*,*Z*), 131.2 (d, *E*,*E*), 131.1 (d, *E*,*E*), 129.6 (d, *E*,*E*), 129.1 (d, *E*,*Z*), 128.5 (d, *E*,*E*), 125.5 (d, *E*,*Z*), 124.5 (d, *E*,*Z*), 64.9 (d), 52.5 (q), 52.0 (d, *E*,*Z*), 51.8 (d, *E*,*E*), 37.4 (t, *E*,*Z*), 37.3 (t, *E*,*E*), 34.6 (t, *E*,*Z*), 34.5 (t, *E*,*E*), 33.0 (t), 18.1 (q, 6 C), 18.0 (q), 12.2 (d, 3 C).

ESI-MS: *m*/*z* (%) = 381 (7) [M$^+$], 270 (78), 207 (85), 192 (100).

Methyl (2*S*,4*R*)-4-Hydroxy-2-[(*E*,*E*)-penta-1,3-dienyl]piperidine-1-carboxylate (18)

A 1.0 M TBAF in THF soln (0.83 mL, 0.83 mmol) was added to a soln of compound **17** (198 mg, 0.52 mmol) in anhyd THF (40 mL) and the resulting mixture was stirred at r.t. for 8.5 h. The solvent was evaporated and the residue was purified by flash chromatography (*n*-hexane–EtOAc, 1.1; R_f = 0.21) to give compound **18** as a 4:1 mixture of the *E*,*E*- and *E*,*Z*-isomers as a colorless oil; yield: 114 mg (97%). The isomers were separated by argentation (silver ion) chromatography[19] (CH_2Cl_2–MeOH, 75:1) to obtain pure (*E*,*E*)-**18** (82 mg, 70%) and (*E*,*Z*)-**18** (19 mg), the latter together with an unidentified impurity.

(*E*,*E*)-18

$[\alpha]_D^{25}$ –36.2 (*c* 0.57, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.09–6.00 (m, 2 H), 5.82 (dd, *J* = 14.1, 5.9 Hz, 1 H), 5.73–5.63 (m, 1 H), 4.85–4.78 (m, 1 H), 4.18–4.13 (m, 1 H), 3.93 (dt, *J* = 13.6, 3.6 Hz, 1 H), 3.70 (s, 3 H), 3.35–3.23 (m, 1 H), 1.96–1.84 (m, 2 H), 1.74 (d, *J* = 6.2 Hz, 3 H), 1.72–1.68 (m, 2 H).

^{13}C NMR (100.4 MHz, $CDCl_3$): δ = 156.2 (s), 130.8 (d), 130.3 (d), 130.2 (d), 129.6 (d), 64.7 (d), 52.6 (q), 50.7 (d), 36.4 (t), 34.2 (t), 31.9 (t), 18.1 (q).

ESI-MS: *m*/*z* (%) = 225 (15) [M$^+$], 224 (13), 206 (66), 191 (85), 148 (100).

Anal. Calcd for $C_{12}H_{19}NO_3$: C, 63.98; H, 8.50; N, 6.22. Found: C, 64.15; H, 8.31; N, 6.07.

(*E*,*Z*)-18

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.40 (ddt, *J* = 15.4, 10.9, 1.4 Hz, 1 H), 6.04–5.92 (m, 2 H), 5.53–5.44 (m, 1 H), 4.91–4.83 (m, 1 H), 4.20–4.15 (m, 1 H), 3.97–3.91 (m, 1 H), 3.71 (s, 3 H), 3.36–3.28 (m, 1 H), 1.99–1.87 (m, 2 H), 1.74 (dd, *J* = 7.2, 1.6 Hz, 3 H), 1.72–1.69 (m, 2 H).

(2*S*,4*R*)-2-[(*E*,*E*)-Penta-1,3-dienyl]piperidin-4-ol (1)[4a]

Carbamate **18** (80 mg, 0.36 mmol) was dissolved in 20% aq MeOH (6 mL) and finely ground KOH (202 mg, 3.6 mmol) was added. The resulting yellowish solution was refluxed for 5 d (TLC monitoring), with the addition of fresh powdered KOH (10 equiv) every 24 h. The mixture was cooled and the solvent was removed under reduced pressure. H_2O (5 mL) was added to the residue and the mixture was extracted with $CHCl_3$ (5 × 5 mL). The combined organic phases were dried over Na_2SO_4, filtered and the solvent was evaporated to obtain crude **1**. Purification on a short silica gel pad (MeOH–EtOAc, 3:2 + 1% NH_4OH; R_f = 0.19) afforded pure, final compound **1** as a white solid; mp 65.5–67.0 °C; yield: 58 mg (97%).

$[\alpha]_D^{24}$ –36.7 (*c* 0.30, $CHCl_3$) {Lit.[4a] $[\alpha]_D^{25}$ –37.0 (*c* 1.0, $CHCl_3$)}.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.16 (dd, *J* = 15.0, 10.3 Hz, 1 H), 6.02 (ddd, *J* = 15.0, 10.3, 1.4 Hz, 1 H), 5.73–5.64 (m, 1 H), 5.55 (dd, *J* = 15.0, 6.4 Hz, 1 H), 3.72–3.64 (m, 1 H), 3.21–3.11 (m, 2 H), 2.69 (td, *J* = 12.7, 2.5 Hz, 1 H), 2.05–1.93 (m, 2 H), 1.85–1.65 (br s, 2 H), 1.75 (d, *J* = 5.5 Hz, 3 H), 1.40 (qd, *J* = 13.1, 4.3 Hz, 1 H), 1.29–1.20 (m, 1 H).

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Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis.

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