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This is the author's manuscript

Original Citation:

Availability:
This version is available http://hdl.handle.net/2318/123502 since 2016-10-18T08:47:34Z

Published version:
DOI:10.1055/s-0032-1317490

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

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Received: 03.08.2012; Accepted after revision: 27.09.2012

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 We have recently shown that the 4-hydroxypyrindine 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-hydroxypipelic 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 1Z,3E-isomer over the 1E,3E-isomer. This required an olefin isomerization by exposure to iodine and a difficult chromatographic separation of the desired isomer from the residual 1Z,3E-compound.5c 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-α-valerolactam (8, 99%) by hydrogenation in methanol over PtO₂ as reported.6 After sequential protection under standard conditions as the TIPS ether 9 (67%) and then the N-CO₂Me 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 chlorophosphite.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-cata-

Figure 1

SYNTHESIS 2012, 44, 3688–3692
Advanced online publication: 24.10.2012
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lyzed 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\(^\circ\).\(^{10,11}\)

In both cases, the reaction provided olefin or with aqueous potassium phosphate as a base (55%).\(^{16}\) of either an aqueous sodium hydroxide solution (98%)\(^{15}\) which was carried out in tetrahydrofuran in the presence of the natural compound \(\{[\alpha]_D^{20} = -13.0\) (c 1.0, CHCl\(_3\))\}.\(^3\) Using the same approach, unnatural (\(+\))-4-epi-SS20846A \(\{[\alpha]_D^{25} = +36.3\) (c 0.41, CHCl\(_3\))\) was prepared in 38% overall yield from (\(S\))-4.

\[\text{Scheme 2 Reagents and conditions: i. TIPSCl, imidazole, DMF, 40 °C, 8 h; ii. CICO}_2\text{Me, n-BuLi, THF, \(-78 °C, 0.5 h; iii. KHMDS, THF, \(-78 °C, 1.5 h; then (PhO)_2P(O)(OPh)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\%),\(^{10,11}\) compound (\(R\))-13 was subjected to heterogeneous hydrogenation to quantitatively give the diastereopure cis-pipelic acid methyl ester derivative 14.\(^{5,8,9}\) Reduction to aldehyde 15 (79%) by diisobutylaluminium 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 \(1^H\) 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\(E,3E\)-stereoisomer, although in a 3.8:1 mixture with a minor isomer which turned out to be, unexpectedly, the 1\(E,3Z\)-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 derivatess of the basis of the number, position and geometry of the double bonds.\(^{19}\) This allowed us to separate the 1\(E,3E\)-isomer (70% yield) from the 1\(E,3Z\)-isomer.

After removal of the \(\text{N}_2\text{CO}_2\text{Me}\) group from 18 by potassium hydroxide in refluxing aqueous methanol, alkald 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 \(\{[\alpha]_D^{20} = \pm 36.3\) (c 0.41, CHCl\(_3\))\}.

In conclusion, we have demonstrated the usefulness of alcohol 4 in the synthesis of 4-hydroxyxypipericine 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 1,4- from the unwanted 1,2-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. CH₂Cl₂ and n-hexane were distilled from CaH₂. Commercial anhyd DMF and MeOH were used. ¹H NMR (400 and 200 MHz) and ¹³C NMR (100.4 and 50.33 MHz) spectra were recorded at 25 °C. Mass spectroscopic analyses were carried out 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 is known, and 13, 14 were prepared as reported for their enantiomers. The lipase-catalyzed kinetic resolution of 4 was carried out as reported.¹⁻³

Preparation of the Silica Gel for Silver Ion Chromatography A 1 M aq soln of AgNO₃ (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 AgNO₃ (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.

Methyl (4R)-2-Oxo-4-(trisopropylsilyloxy)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 (0.062 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 NaHCO₃ (6 mL) and the mixture was extracted with CH₂Cl₂ (3 × 6 mL). The combined organic extracts were dried over Na₂SO₄, 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%).

Methyl (2S,4R)-2-Formyl-4-(trisopropylsilyloxy)piperidine-1-carboxylate (15) A soln of ester 14 (374 mg, 1.0 mmol) in anhyd CH₂Cl₂ (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. After an additional 2 h, the reaction was quenched by adding anhyd MeOH (1.2 mL, 1.2 mmol) and sat. aq NH₄Cl (30 mL) was added. The mixture was diluted with CH₂Cl₂ (30 mL) and the product was extracted with CH₂Cl₂ (3 × 20 mL); the combined organic phases were dried over Na₂SO₄, 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.

Methyl (2S,4R)-2-[(E)-2-iodovinyl]-4-(trisopropylsilyloxy)piperidine-1-carboxylate (16) A soln of aldehyde 15 (270 mg, 0.79 mmol) and CH₄ (590 mg, 1.50 mmol) in anhyd THF (4 mL) was added dropwise to a green suspension of CrCl₂ (553 mg, 4.50 mmol) in anhyd THF (11 mL) cooled to 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 Et₂O (6 × 30 mL). The combined organic phases were dried over Na₂SO₄, 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%).
A soln of the Pd/PtPhs catalyst was prepared by mixing Pd(OAc)₂ (5.90 mg, 0.026 mmol) and PtPhs (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, 5.0 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 H₂O (30 mL), dried over Na₂SO₄ and filtered, and the solvent was evaporated to obtain crude 17. Purification by flash chromatography (n-hexane–EtOAc, 12:1; Rf = 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%).

1H NMR (400 MHz, CDCl₃): 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 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, E), 3.93–3.82 (m, 1 H, E), 3.70 (s, 3 H, E,E), 3.58 (s, 3 H, E,Z), 3.42–3.32 (m, 1 H, E), 1.88–1.81 (m, 2 H, E), 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), 1.05 (s, 21 H, E).

13C NMR (100.4 MHz, CDCl₃): δ = 156.1 (s), 133.6 (d, E,Z), 131.2 (d, E,E), 131.1 (d, E,E), 126.9 (d, E,E), 129.1 (d, E,E), 128.5 (d, E,E), 125.5 (d, E,Z), 124.5 (d, E,Z), 64.9 (d, 52.5 (q, d, E,E), 51.8 (d, E,E), 37.4 (t, E,E), 37.3 (t, E,E), 34.6 (t, E,E), 34.5 (t, E,E), 33.0 (t), 18.1 (q, C), 18.0 (q, 12.2 (d, C).

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

Methyl (2S,4R)-4-Hydroxy-2-[(E,E)-penta-1,3-dienyl]piperidino-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; Rf = 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)⁴ (CH₂Cl₂–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.

Acknowledgment
Dr. Maurizio Passaponti is acknowledged for technical assistance, and Ente Cassa di Risparmio di Firenze for granting a 400-MHz NMR spectrometer.

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

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J. Org. Chem. 2010, 5831. (c) Optical rotation values for (R)-13: $[\alpha]_D^{24} +127.1$ (c 0.64, CHCl$_3$); for (2S,4R)-14: $[\alpha]_D^{23}$ $-11.9$ (c 0.45, CHCl$_3$).


(7) The preparation of the lactam-derived enol phosphate and subsequent palladium-catalyzed methoxycarbonylation were carried out as reported in ref. 5b, but the latter at 75 °C and with 80 equivalents of MeOH.


(9) The formation of the unwanted compound 11 is easily revealed by the multiplets at 5.99–5.93 ppm (1 H) and 5.66–5.58 ppm (2 H) assignable to the olefinic protons of 11 in the $^1$H NMR spectrum of the mixture.


(11) As an alternative to the scalable kinetic resolution, it is possible to also carry out the enantiomeric separation by semipreparative HPLC, which allows 1 mmol of each enantiomer, with ee higher than 99.9%, to be obtained: Chiralpack IC semipreparative column (10 × 250 mm, 5 μm, Daicel, Osaka, Japan), isocratic elution with heptane–EtOH (7:3), flow 4.7 mL/min. Analytical: Chiralpak IC column (4.6 × 250 mm, 5 μm) at 1 mL/min. Retention times: (R)-4 (7.69 min), (S)-4 (12.74 min).


(17) Aldrich 701831. In the $^1$H NMR (CDCl$_3$) spectrum of the commercial compound, the cis-isomer has diagnostic signals at 6.37 (m) and 5.26 (dq) ppm.

(18) In compound 18, as well as in compounds 14–17, the two piperidine ring substituents are axially oriented, as shown by the low coupling constant values for the equatorial protons at C2 and C4 (highest is 6.6 Hz for 2-H in the aldehyde) as well as the lack of NOE effect between 2-H and 4-H with axial 6-H. This is due to the presence of the N-protection which forces the substituent at C2 into an axial orientation to remove the A(1,3) strain with it; see: Comins, D. L.; Joseph, S. P. In Advances in Nitrogen Heterocycles; Vol. 2; Moody, C. J., Ed.; JAI Press: Greenwich, CT, 1996, 251–294.