Total Synthesis of Sperabillin A and C

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Dedicated to Prof. Dr. Dr. h.c. Fritz Eiden on the occasion of his 80th birthday.

Abstract: The first total synthesis of sperabillin A and an improved total synthesis of sperabillin C have been achieved in 11 steps from *N*-Boc-*O*-methyl-L-tyrosine. The stereoselective pathway to the core (3*R*,5*R*)-3,6-diamino-5-hydroxyhexanoic acid involves an Arndt–Eistert homologation, an asymmetric Henry reaction and a ruthenium tetroxide-catalyzed oxidative degradation of a benzene ring as key steps.

Key words: sperabillins, antibiotics, pseudo-peptides, Henry reaction, ruthenium tetroxide

(3*R*,5*R*)-3,6-Diamino-5-hydroxyhexanoic acid (**1**, Figure 1) is the core fragment of the pseudo-peptide antibiotics negamycin (**2**) and sperabillin A and C (**3a** and **3c**, respectively). Negamycin (**2**), isolated in 1970 from culture filtrates of strains closely related to *Streptomyces purpeofuscus* by Umezawa et al., shows potent growth-inhibitory activity against Gram-negative bacteria.[1] By contrast sperabillin A (**3a**), the main member of the sperabillin family of antibiotics, which was isolated in 1986 from the culture broth of *Pseudomonas fluorescens* YK-437 by researchers at Takeda Chemical Industries Ltd., exerts promising in vitro and in vivo antibacterial activity especially against Gram-positive pathogens, including multiresistant strains of *Staphylococcus aureus*.[2] While there are numerous reports in the literature concerning the synthesis of negamycin (**2**), both in racemic and optically active form,[3] little attention has been given to the synthesis of sperabillin A (**3a**) and C (**3c**) incorporating the same core β,ε-diamino acid. Only one total synthesis of sperabillin C (**3c**; 15 steps starting from *N*-Boc-glycine, 2.5% overall yield) has been reported to date.[4,5]

In this communication, we describe the first total synthesis of sperabillin A (**3a**) as well as an improved total synthesis of sperabillin C (**3c**). Our approach toward these antibiotics and analogues with modified fragments attached to the N^{ε}- and C-terminal regions is based on the orthogonally protected β,ε-diamino acid **4**. As outlined in Scheme 1 building block **4** was envisioned to be readily accessible from *N*-Boc-L-tyrosine derived aldehyde **6** by two key transformations: (a) stereoselective Henry reaction to give β-nitro alcohol **5** and (b) oxidative degradation of the phenyl ring, which serves as a masked

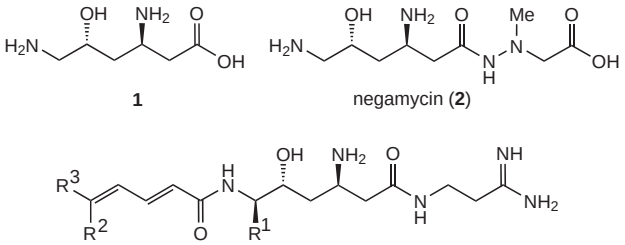
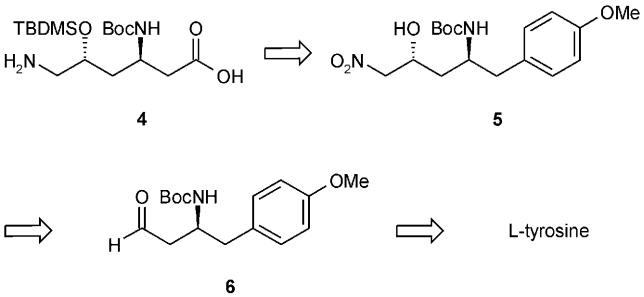


Figure 1

carboxylic acid, and subsequent reduction of the nitro group.

Aldehyde **6** was readily obtained from commercially available *N*-Boc-*O*-methyl-L-tyrosine (**7**) in two steps (Scheme 2). Arndt–Eistert homologation of the α-amino acid **7** following a standard protocol[6] afforded β-amino ester **8** {$[\alpha]_D^{23}$ –9.3 (*c* 0.8 in CH_2Cl_2); lit.[7] (*R*)-**8**: $[\alpha]_D$ +9.2 (*c* 1.2 in CH_2Cl_2)}, which subsequently was reduced with DIBAL-H (toluene, –85 °C) to give **6** in 73% overall yield. Previous studies conducted in this and other laboratories have indicated that it is difficult to achieve control of stereochemistry for Henry reactions of nitromethane with chiral aldehydes like **6** bearing the inducing stereogenic center in the β-position.[8] Therefore we envisioned the application of a chiral catalyst, namely Evans' bis(oxazoline) copper(II) acetate-based catalyst (+)-**11**,[9] to control the configuration of the newly created stereogenic center at C-5.[8c] Indeed, Henry reaction of nitromethane with aldehyde **6** in the presence of 5 mol% of (+)-**11**



Scheme 1

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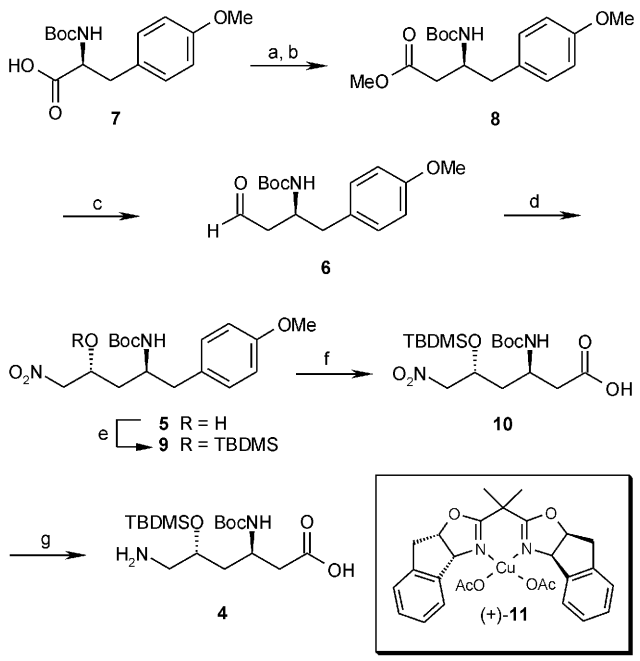
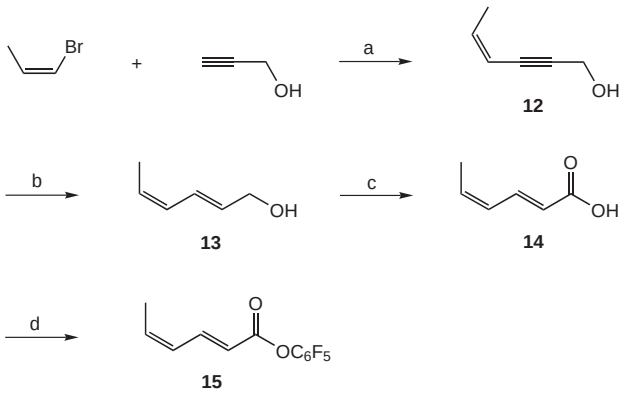


Scheme 2 *Reagents and conditions*: (a) i) isobutyl chloroformate, NMM, DME, –20 °C; ii) CH_2N_2, –20 °C to r.t.; (b) silver benzoate, Et_3N, MeOH, r.t. (86%, two steps); (c) DIBAL-H, toluene, –85 °C (85%); (d) $MeNO_2$, (+)-**11** (5 mol%), EtOH, r.t. (83%); (e) TBDMSCl, imidazole, DMF, r.t. (82%); (f) RuO_2 (5 mol%), $NaIO_4$, $NaHCO_3$, EtOAc–H_2O, r.t. (67%); (g) HCO_2NH_4, Pd/C, MeOH, r.t. (90%)

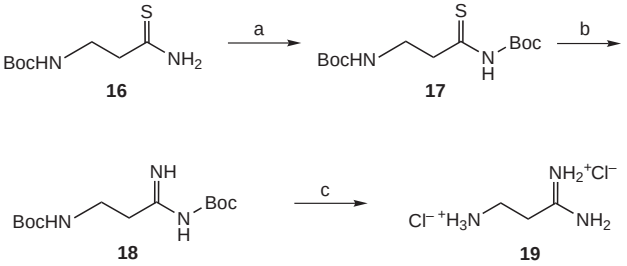
(EtOH, r.t., 3 d) afforded the desired β-nitro alcohol **5** with both high diastereoselectivity (95% de)[10] and yield (83%).

After protecting the secondary alcohol as a *tert*-butyldimethylsilyl (TBDMS) ether we turned our attention to the oxidative degradation of the 4-methoxyphenyl ring. Ruthenium tetroxide-catalyzed degradation of aromatic rings to carboxylic acids has been repeatedly applied as a useful tool in the synthesis of amino acids and peptides.[11] However, *N*-acylamines bearing a primary alkyl goup at the nitrogen were reported to undergo facile oxidation at the α-position to give the corresponding imides.[12] Accordingly, the aromatic ring has to be cleaved prior to the generation of the C-6 amino group assuming that the nitro group would act as a 'protective group' for amines during ruthenium tetroxide oxidations. Indeed ruthenium tetroxide-catalyzed degradation of **9** afforded the desired ε-nitro carboxylic acid **10** in good yield (67%). Best results were obtained using catalytic amounts of ruthenium dioxide (5 mol%) and an excess of sodium metaperiodate (30 equiv) in a two-phase system of ethyl acetate and water at room temperature according to Yoshifuji et al.[12,13] To avoid cleavage of the acid labile protecting groups due to pH decrease during the oxidation sodium hydrogen carbonate was added.[14] Finally, catalytic reduction of the nitro group with ammonium formate in the presence of Pd/C afforded the desired amino acid **4**[15] in 90% yield.

(2*E*,4*Z*)-Hexa-2,4-dienoic acid (**14**), representing the N^{ε}-acyl residue of sperabillin A (**3a**) and B (**3b**), was prepared in four steps, starting with a Sonogashira coupling of (*Z*)-1-bromoprop-1-ene and propargylic alcohol [$(Ph_3P)_2PdCl_2$ (0.25 mol%), CuI (1.5 mol%), Ph_3P, *n*-$PrNH_2$, Et_2O, Δ) to give (*Z*)-hex-4-en-2-yn-1-ol (**12**)[16] in 69% yield (*Z*:*E* > 99:1; Scheme 3).[17] This product was stereoselectively reduced with $LiAlH_4$ (THF, Δ)[18] providing (2*E*,4*Z*)-hexa-2,4-dien-1-ol (**13**) in 94% yield [(2*E*,4*Z*):(2*Z*,4*Z*) > 99:1]. Oxidation of **13** was then accomplished by a one-pot, two-step procedure. First, the allylic alcohol **13** was oxidized with manganese dioxide (pentane, r.t.) to give the corresponding aldehyde, which was further oxidized by the addition of silver nitrate (KOH, EtOH–H_2O, r.t.) to afford diastereoisomerically pure (2*E*,4*Z*)-2,4-hexadienic acid (**14**) in 77% overall yield. Finally, the carboxylic acid **14** was converted into the corresponding pentafluorophenyl ester **15** (C_6F_5OH, EDC, CH_2Cl_2, r.t.) in 94% yield.



Scheme 3 *Reagents and conditions*: (a) $(Ph_3P)_2PdCl_2$, CuI, Ph_3P, *n*-$PrNH_2$, Et_2O, Δ (69%); (b) $LiAlH_4$, THF, Δ (94%); (c) (i) MnO_2, pentane, r.t. (ii) $AgNO_3$, KOH, Et_2O–H_2O, r.t. (77%); (d) C_6F_5OH, EDC, CH_2Cl_2, 0 °C (94%)



Scheme 4 *Reagents and conditions*: (a) (i) NaH (2.1 equiv), $(Boc)_2O$, THF, –78 °C to –40 °C (88%); (b) NH_3, EtOH, 0 °C (99%); (c) HCl, Et_2O, 0 °C to r.t. (quant.)

3-Aminopropionamidine, the fragment common to all members of the sperabillin family of antibiotics and also part of a number of other antibiotics (e.g. distamycin A or amidinomycin), was prepared in three steps, starting from readily available *N*-Boc-β-alanine thioamide (**16**,[19] Scheme 4).[20] First, the thioamide **16** was acylated with di-*tert*-butyl dicarbonate in the presence of 2.1 equivalents of sodium hydride (THF, –78 °C to –40 °C)[21] to afford *N*-Boc thioamide **17** in 88% yield. Secondly, **17** was readily converted into the corresponding *N*-Boc amidine **18** by

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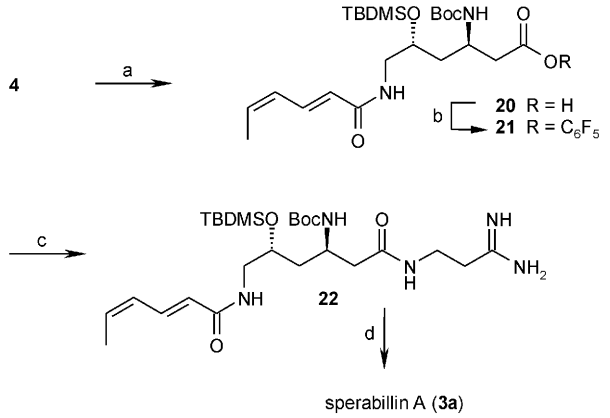
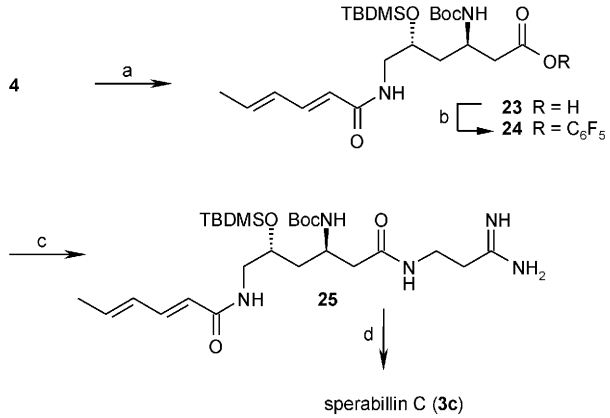
treatment with NH_3 in ethanol at 0 °C (99% yield). Removal of the *tert*-butoxycarbonyl protecting groups with 2.0 M ethereal HCl then led to 3-aminopropionamidine dihydrochloride (**19**) in quantitative yield.

With the three building blocks **4**, **15** and **19** in hand sperabillin A (**3a**) was readily assembled in four steps (Scheme 5). First, the ε-amino group was acylated with pentafluorophenyl ester **15** (Et_3N, DMF, r.t.) to give amide **20** in 71% yield. Subsequently, **20** was activated as a pentafluorophenyl ester (C_6F_5OH, EDC, CH_2Cl_2, r.t.) and then coupled with 3-aminopropionamidine dihydrochloride (**19**) (Et_3N, DMF, r.t.) to afford **22** in 82% yield (two steps). Finally, the acid-labile protecting groups were removed by treatment with TFA (5% H_2O, r.t.) to afford, after anion exchange on Amberlite® IRA 402 Cl resin, sperabillin A dihydrochloride (**3a**)[22] in 92% yield. The spectroscopic data for **3a** were in full agreement with those reported for the natural product.[2c] In the end, sperabillin C (**3c**)[23] was prepared analogously to **3a** in 20% overall yield from **4**, (2*E*,4*E*)-hexa-2,4-dienoic acid pentafluorophenyl ester and **19** (Scheme 6).



Scheme 5 *Reagents and conditions*: (a) **15**, Et_3N, DMF, r.t. (71%); (b) C_6F_5OH, EDC, CH_2Cl_2, r.t.; (c) **19**, Et_3N, DMF, r.t. (82%, two steps); (d) TFA, H_2O (5%), r.t. (92%)



Scheme 6 *Reagents and conditions*: (a) (2*E*,4*E*)-hexa-2,4-dienoic acid pentafluorophenyl ester, Et_3N, DMF, r.t. (83%); (b) C_6F_5OH, EDC, CH_2Cl_2, r.t.; (c) **19**, Et_3N, DMF, r.t. (87%, two steps); (d) TFA, H_2O (5%), r.t. (94%)

In summary, the first total synthesis of the pseudopeptide antibiotic sperabillin A (**3a**) as well as a markedly improved total synthesis of sperabillin C (**3c**) have been accomplished [11 steps from *N*-Boc-*O*-methyl-L-tyrosine (**7**), 16% and 20% overall yield, respectively]. Our concise and inherently flexible approach seems to be quite attractive for the generation of libraries of sperabillin A and C analogues for biological evaluation.

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(10) The reaction of chiral aldehyde **6** with nitromethane in the presence of catalyst (+)-**11** represents the matched case of double diastereoselection, since application of the enantiomeric catalyst (–)-**11** gave the corresponding epimer of **5** with slightly lower stereoselectivity (91% de).

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(13) (a) In addition to product **10**, its *N*-formyl derivative 3-*tert*-butoxycarbonylformylamino-5-*tert*-butyldimethylsilyloxy-6-nitrohexanoic acid (5% yield) and trace amounts (<1%) of 4-*tert*-butoxycarbonylamino-2-*tert*-butyldimethylsilyloxyhexanedioic acid, the latter indicating a Nef-type reaction at the nitromethyl group, were obtained. Application of the reaction conditions [2.2 mol% RuCl, $NaIO_4$ (18 equiv), CCl_4–MeCN–H_2O = 2:2:3, r.t.] previously developed by Sharpless and co-workers (see ref. 13b) gave the oxidation product **10** in a 41% yield together with 24% of the *N*-formyl derivative mentioned above. (b) Carlsen, P. H. J.; Katsuki, T.; Martin, V. S.; Sharpless, K. B. *J. Org. Chem.* **1981**, *46*, 3936.

(14) In the absence of sodium hydrogen carbonate a somewhat lower yield (56%) of product **10** was obtained.

(15) Spectroscopic data of compound **4**: $[\alpha]_D^{20}$ +20.8 (*c* 0.95 in CH_2Cl_2). ^{1}H NMR (500 MHz, MeOH-d_4): δ = 0.13 (3 H, s), 0.15 (3 H, s), 0.92 (9 H, s), 1.43 (9 H, s_{br}), 1.78 (2 H, m), 2.31 (1 H, dd, *J* = 14.9, 7.7 Hz), 2.39 (1 H, dd, *J* = 14.9, 4.7 Hz), 3.01 (1 H, dd, *J* = 13.0, 4.1 Hz), 3.06 (1 H, dd, *J* = 13.0, 4.9 Hz), 3.85 (1 H, m), 4.18 (1 H, m), 4.09 (1 H, m). ^{13}C NMR (100 MHz, MeOH-d_4): δ = –5.0, 18.4, 25.9, 28.3, 40.0, 43.5, 45.2, 45.8, 67.7, 79.6, 157.1, 178.6.

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(22) Spectroscopic data of sperabillin A (**3a**)[2c]: $[\alpha]_D^{23}$ –11.4 (*c* 0.4 in H_2O), lit.[2c] $[\alpha]_D^{23}$ –11 (*c* 1.1 in H_2O). ^{1}H NMR (500 MHz, D_2O): δ = 1.77 (1 H, ddd, *J* = 4.5, 10.0, 15.0 Hz), 1.87 (3 H, d, *J* = 7.2 Hz), 1.87 (1 H, m), 2.68 (2 H, t, *J* = 6.6 Hz), 2.74 (2 H, m), 3.33 (1 H, dd, *J* = 6.6, 14.0 Hz), 3.39 (1 H, dd, *J* = 4.5, 14.0 Hz), 3.55 (1 H, dt, *J* = 6.6, 14.0 Hz), 3.59 (1 H, dt, *J* = 6.7, 14.0 Hz), 3.86 (1 H, m), 4.00 (1 H, m), 6.02 (1 H, dq, *J* = 7.2, 10.8 Hz), 6.07 (1 H, d, *J* = 15.1 Hz), 6.23 (1 H, t, *J* = 10.8 Hz), 7.56 (1 H, dd, *J* = 11.8, 15.1 Hz). ^{13}C NMR (100 MHz, D_2O): δ = 16.0, 35.3, 38.0, 39.2, 39.8, 47.8, 49.1, 69.1, 125.1, 129.6, 139.4, 139.5, 171.7, 172.4, 174.7.

(23) Spectroscopic data of sperabillin C (**3c**)[2c]: $[\alpha]_D^{23}$ –10.2 (*c* 0.4 in H_2O), lit.[2c] $[\alpha]_D^{20}$ –11 (*c* 0.7 in H_2O). ^{1}H NMR (500 MHz, D_2O): δ = 1.75 (1 H, ddd, *J* = 4.7, 10.0, 15.0 Hz), 1.83 (3 H, d, *J* = 5.5 Hz), 1.87 (1 H, ddd, *J* = 3.1, 7.5, 15.0 Hz), 2.67 (2 H, t, *J* = 6.7 Hz), 2.73 (2 H, d, *J* = 7.0 Hz), 3.30 (1 H, dd, *J* = 6.5, 14.0 Hz), 3.37 (1 H, dd, *J* = 4.7, 14.0 Hz), 3.57 (2 H, m), 3.85 (1 H, m), 3.98 (1 H, m), 5.97 (1 H, d, *J* = 15.5 Hz), 6.26 (2 H, m), 7.13 (1 H, dd, *J* = 9.7, 15.5 Hz). ^{13}C NMR (100 MHz, D_2O): δ = 20.7, 35.3, 38.0, 39.2, 39.8, 47.8, 49.1, 69.1, 122.9, 132.0, 143.2, 145.4, 171.6, 172.5, 174.7.

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