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Isolation, Enantioselective Total Synthesis and Structure Determination of the Anthrapyran Metabolite SS 43405-e

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The first enantioselective total synthesis of the anthrapyran metabolite SS 43405-e, isolated from a marine-derived streptomycete, is described, which also allows the determination of the so far unknown absolute (*R*) configuration of the natural product. For the synthesis the bromoanthracene derivative **3** is lithiated and coupled with the enantiopure aldehyde (*S*)-**4** to give **9**, which is oxidatively transformed into the corresponding anthraquinone **10** and further into the ketone **2**. The final step is the cyclization of **2** under acidic conditions to give the desired antibiotic (*S*)-**1**.

Introduction

The anthrapyran metabolite SS 43405-e (**1**) (Figure 1) was first isolated by Masaru et al. in 1986.[1] Its constitution was determined by spectroscopic methods, however, the absolute configuration of the single stereogenic center remained unknown. Total syntheses of **1** have not been performed so far and investigations of the biological activity of this antibiotic was hampered by lack of material. Recently, we have found a new approach towards the preparation of anthrapyran antibiotics, which for the first time allowed the enantioselective synthesis of chiral members of this class of natural products.[2] Recently, also Krohn et al.[3] has developed a new procedure which can be used for the formation of chiral anthrapyrans.

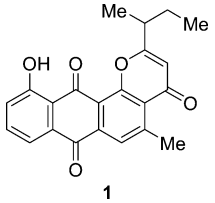

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Figure 1. Proposed structure of anthrapyran metabolite SS 43405-e (**1**).

Here, we describe the first enantioselective total synthesis of (14*S*)-SS 43405-e (*S*)-**1**, which allowed us to confirm the proposed structure and to determine the stereochemistry of the natural compound.

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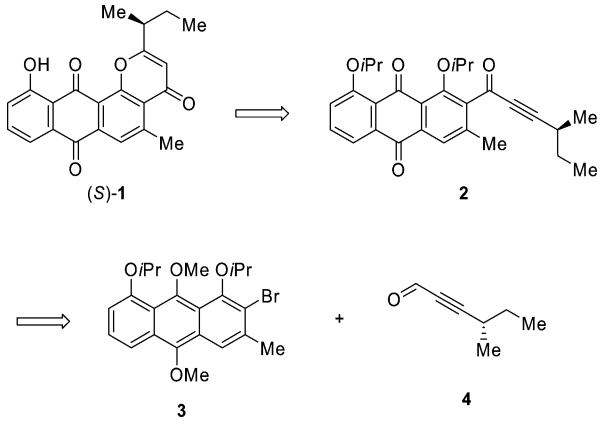
Results and Discussion

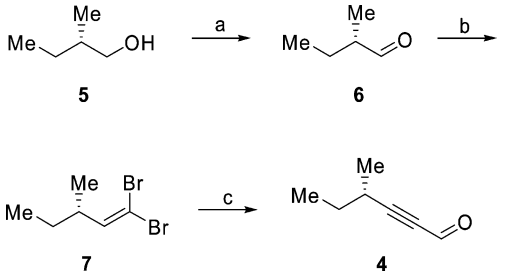
The retrosynthetic analysis of (14*S*)-SS 43405-e (**1**) is outlined in Scheme 1. The first disconnection in the pyrone ring moiety envisions an intramolecular 6-*endo*-digonal cyclization of the ynone derivative **2** in a domino process.[4]



Scheme 1. Retrosynthetic analysis of (14*S*)-SS 43405-e (*S*)-**1**.

The required substrate **2** should result from a nucleophilic attack of an aryllithium species generated from the bromodimethoxyanthracene derivative **3** onto the propargylic aldehyde **4**.

For the synthesis of **4**, commercially available (*S*)-2-methyl-1-butanol (**5**) was oxidized utilizing Swern conditions[5] to furnish the aldehyde **6** in 80% yield. Subsequent Corey–Fuchs homologation afforded the vinyl dibomide **7** in 79% yield.[6] Treatment of **7** with *n*BuLi followed by formylation with *N*,*N*-dimethylformamide furnished the propargylic aldehyde **4** in 76% yield (Scheme 2).[7]



Scheme 2. Reagents and conditions: a) oxalyl chloride, DMSO, CH_2Cl_2, Et_3N, 2 h, 80%; b) PPh_3, CBr_4, Zn, CH_2Cl_2, room temp., 13 h, 79%; c) *n*BuLi, THF, DMF, –78 °C to 0 °C, 4 h, 76%.

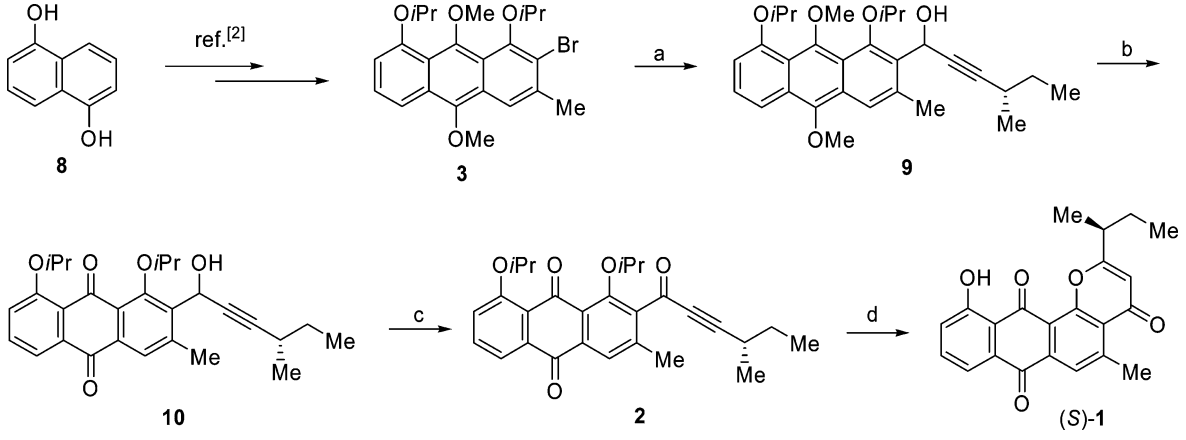
The next task was the coupling of propargylic aldehyde **4** with the bromodimethoxyanthracene derivative **3** (Scheme 3). In an earlier report we have shown that **3** can easily be prepared in a highly efficient manner starting from commercially available 1,5-dihydroxynaphthalene **8** (7 steps, 37% overall yield).[2] After conversion of **3** into the corresponding lithium derivative by a bromine lithium exchange using *n*BuLi at low temperature, the subsequent reaction with the propargylic aldehyde **4** proceeded smoothly to give the corresponding alcohol **9** in 78% yield as a mixture of both possible diastereomers. At this stage the missing selectivity has no consequences since the formed stereogenic center is later removed by oxidation. It was important to add the aldehyde **4** immediately after generation of the organolithium compound to avoid the formation of the corresponding debrominated compound as side product. Oxidative demethylation of anthracene derivative **9** by means of $Ag^{II}O/HNO_3$[8] yielded the anthraquinone derivative **10** in 92% yield, which was subsequently subjected to IBX oxidation[9] to afford the ynone derivative **2** in 96% yield. The next task was to remove the protecting groups at the anthraquinone moiety and perform the ring closure via an intramolecular 6-*endo-dig* cyclization to yield the desired final product under acidic conditions in a domino process.[4] Thus, the treatment of a solution of **2** in acetic acid at 60 °C with a catalytic amount of sulfuric acid led to cleavage of both the isopropyl ethers followed by intramolecular 6-*endo-dig* cyclization[10] to yield (*S*)-SS 43405-e (***S*)-1** in 81% yield.

Since the antibiotic SS 43405-e could not be obtained from Masaru et al.[1] for comparison, we isolated the natural product from the culture broth of the marine-derived streptomycete isolate B5543.[11] The incubation was performed at 28 °C in a 20 L fermenter for 72 h to afford 1.60 g of crude material by extraction with ethyl acetate. Chromatography on silica gel furnished three fractions. Repeated PTLC of fraction 1 finally gave 10.3 mg of pure SS 3405-e (**1**). The ^1H NMR spectra of the isolated natural product **1** and synthetic compound (*S*)-**1** are identical in all respects, including chemical shifts as well as coupling constant values. The absolute configuration of the stereogenic center in the natural product was determined by comparison of the optical rotations. The $[\alpha]_D^{20}$ value of the synthetic compound (*S*)-**1** was determined as +4.8 (*c* = 0.3, DMSO), which is opposite in sign to the $[\alpha]_D^{20}$of the natural sample with $[\alpha]_D^{20}$ = –5.2 (*c* = 0.4, DMSO). This clearly indicates that the stereogenic center of natural SS 43405-e has (*R*) configuration.

In conclusion, we have developed an enantioselective total synthesis of the novel anthrapyran antibiotic SS 43405-e (*S*)-**1**, which allowed us to determine the absolute configuration of the natural product as (*R*)-**1**. For the comparison SS 43405-e was isolated from the culture broth of the marine-derived streptomycete isolate B5543.

Experimental Section

General: All reactions were performed in flame-dried glassware under an atmosphere of argon and the reactants were introduced by syringe. Solvents were dried and purified according to the method defined by Perrin and Armarego.[12] Commercial reagents were used without further purification. Thin-layer chromatography (TLC) was carried out on precoated Alugram SIL G/UV_{254} (0.25 mm) plates from Macherey–Nagel & Co. Column chromatography was carried out on silica gel 60 from Merck with particle size 0.063–0.200 mm for normal pressure and 0.020–0.063 mm for flash chromatography (P = pentane). Melting points were recorded on a Mettler FP61 and are uncorrected. IR spectra were determined on



Scheme 3. Reagents and conditions: a) *n*BuLi, THF, –78 °C, 10 min, 78%; b) $Ag^{II}O$, dioxane, 4 N HNO_3, room temp., 30 min, 92%; c) IBX, CH_2Cl_2, DMSO, room temp., 4 h, 96%; d) AcOH, cat. H_2SO_4, 60 °C, 1.5 h, 81%.

a Bruker Vektor 22 (KBr pellets or films), UV/Vis spectra on a Perkin–Elmer Lambda 2 (CH_3CN), and mass spectra on a Finnigan MAT 95, and a Bioapex fourier transformation ion cyclotron resonance mass spectrometer for ESI-HRMS. ^1H NMR spectra were recorded either on a Varian Mercury 300, Unity 300 or Inova 600 spectrometer. ^{13}C-NMR spectra were recorded at 50 or 75 MHz. Spectra were taken at room temperature in deuterated solvents as indicated using the solvent peak or TMS as internal standard.

Compound 6: To a stirred solution of oxalyl dichloride (4.32 mL, 50.0 mmol) in CH_2Cl_2 (100 mL) was added at –78 °C within 20 min a solution of DMSO (6.10 mL, 100 mmol) and (*S*)-2-methyl-1-butanol (**5**, 4.8 mL, 45 mmol) in CH_2Cl_2 (40 mL). Stirring was continued for 15 min, then Et_3N (31.8 mL, 226 mol) was added dropwise and stirring continued for another 15 min. The solution was allowed to reach 20 °C within 1 h. Afterwards, H_2O was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 × 100 mL). The combined organic phases were washed with aqueous HCl (2%) and then with aqueous Na_2CO_3 solution (5%). After drying over Na_2SO_4 and filtration, the solvent and dimethylsulfide were carefully removed by distillation using a Vigreux column (30 cm). The residue was distilled using a 15 cm Vigreux column to yield the aldehyde **6** (3.10 g, 80%) as a colourless liquid, which was directly used for the next step. B.p. 90–92 °C. $[\alpha]_D^{20}$ = +37.6 (c = 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.63 (d, J = 2.0 Hz, 1 H, CHO), 2.34–2.22 (m, 1 H, 2-H_1), 1.82–1.67 (m, 1 H, 4-H_a), 1.51–1.36 (m, 1 H, 4-H_b), 1.10 (d, J = 7.0 Hz, 3 H, 3-H_3), 0.96 (t, J = 7.5 Hz, 3 H, 5-H_3) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 205.4, 47.73, 23.49, 12.83, 11.33 ppm.

Compound 7: To a stirred mixture of CBr_4 (13.2 g, 40.0 mmol) and zinc (2.60 g, 40.0 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added Ph_3P (10.5 g, 40.0 mmol) in CH_2Cl_2 (25 mL) and stirring was continued at room temp. for 60 min. After cooling to 0 °C a solution of the aldehyde **6** (1.72 g, 20.0 mmol) in CH_2Cl_2 (25 mL) was added. The reaction mixture was stirred at room temp. for 12 h and then diluted with pentane with vigorous stirring. A precipitate was formed which was removed by filtration through Florisil. The filterate was concentrated under reduced pressure (600 mbar) to yield the crude residue which was fractionally distilled to give the compound **7** (3.82 g, 79%) as a colourless liquid. B.p. 84–86 °C (48 mbar). $[\alpha]_D^{20}$ = +14.3 (c = 2.0, heptane). ^1H NMR (300 MHz, $CDCl_3$): δ = 6.16 (d, J = 9.3 Hz, 1 H, 2-H_1), 2.48–2.30 (m, 1 H, 3-H_1), 1.45–1.29 (m, 2 H, 5-H_2), 1.01 (d, J = 6.7 Hz, 3 H, 4-H_3), 0.90 (t, J = 7.5 Hz, 3 H, 6-H_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 144.22, 87.31, 39.90, 28.96, 18.84, 11.63 ppm. MS (EI): *m*/*z* (%) = 243 (62), 241 (100), 239 (50), 235.1 (20).

Compound 4: To a stirred solution of compound **7** (484 mg, 2.00 mmol) in THF (8.0 mL) at –78 °C was added *n*BuLi (2.5 M in hexane, 1.6 mL, 4.0 mmol). After being warmed to –20 °C over 2 h, the mixture was cooled to –78 °C and DMF (0.10 mL) was added. After being gradually warmed to room temp. over 2 h, the mixture was quenched by the addition of aqueous saturated NH_4Cl solution. The reaction mixture was diluted with diethyl ether and washed with water, brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure (200 mbar) to afford the crude product which was purified by chromatography on silica gel. Elution with pentane provided product **4** (167 mg, 76%) as a liquid. $[\alpha]_D^{20}$ = +12.2 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ = 9.21 (s, 1 H, CHO), 2.65–2.53 (m, 1 H, 4-H_1), 1.62–1.46 (m, 2 H, 6-H_2), 1.24 (d, J = 6.9 Hz, 3 H, 5-H_3), 1.02 (t, J = 8.4 Hz, 3 H, 7-H_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 177.47, 102.92, 81.70, 28.87, 27.88, 19.24, 11.34 ppm. $\tilde{\nu}$ = 2874, 2232, 1566, 1460, 1097 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 284.5 nm (3.295). MS (DCI): *m*/*z* (%) = 128.1 (82) $[M + NH_4]^+$, 110.1 (100) $[M + H]^+$.

Compound 9: To a stirred solution of compound **3** (223 mg, 0.50 mmol) in THF (2.5 mL) at –78 °C was added *n*BuLi (2.5 M in hexane, 0.23 mL, 0.57 mmol) followed by propargylic aldehyde **4** (66 mg, 0.6 mmol) dissolved in THF (0.5 mL). Stirring was continued at –78 °C for 10 min and the reaction was quenched by the addition of aqueous saturated NH_4Cl solution. The reaction mixture was diluted with CH_2Cl_2 and washed with water, brine and dried with Na_2SO_4. The solvent was evaporated under reduced pressure to afford the crude product which was purified by chromatography on silica gel. Elution with 10% EtOAc/pentane provided product **9** (186 mg, 78%) as a viscous oil. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.85–7.79 (m, 4 H, 2 × 5′-H, 2 × 4′-H), 7.36–7.30 (m, 2 H, 2 × 6′-H), 6.82 (d, J = 7.1 Hz, 2 H, 2 × 7′-H), 6.60–6.07 (br. s, 2 H, 2 × 1-H), 4.76–4.51 (m, 4 H, 2 × C-1′-OC*H*$(CH_3)_2$, 2 × C-8′-OC*H*$(CH_3)_2$), 4.04 (s, 6 H, 2 × OMe), 3.79 (s, 6 H, 2 × OMe), 2.92–2.69 (br. s, 6 H, 2 × Ar-CH_3), 2.48–2.34 (m, 2 H, 2 × 4-H), 1.58–1.22 (m, 28 H, 2 × 6-H_2, 2 × C-1′-OCH(C*H*$_3)_2$, 2 × C-8′-OCH(C*H*$_3)_2$), 1.14 (d, J = 7.3 Hz, 6 H, 2 × 5-H_3), 0.95 (t, J = 7.6 Hz, 6 H, 2 × 7-H_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 154.82, 150.32, 146.89, 130.18, 127.96, 126.61, 125.60, 119.88, 118.85, 115.18, 109.91, 90.66, 77.35, 71.94, 63.37, 62.57, 29.70, 27.70, 21.95, 21.88, 20.70, 20.38, 11.77 ppm. $\tilde{\nu}$ = 2971, 2930, 2873, 1616, 1556, 1511 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 201.5 (4.385), 229.5 (4.172), 268.0 (4.876), 380.0 (3.865), 398.0 (3.758), 420.5 (3.610), 363.0 nm (3.609). HRMS (ESI): calcd. for $C_{30}H_{38}O_5$ + Na^+: 501.26115; found: 501.26098.

Compound 10: To a stirred solution of compound **9** (167 mg, 0.35 mmol) in dioxane (7 mL) was added $Ag^{II}O$ (216 mg, 1.75 mmol) followed by 4 N HNO_3 until the silver oxide has completely dissolved. The resulting solution was stirred for 30 min and then diluted with CH_2Cl_2. The organic layer was washed with water, brine, dried with Na_2SO_4 and the solvent evaporated under reduced pressure to afford the crude product which was purified by silica gel chromatography using 20% EtOAc/pentane as the eluent to yield compound **10** (143 mg, 92%) as a viscous oil. ^1H NMR (600 MHz, $CDCl_3$): δ = 7.76–7.74 (m, 4 H, 2 × 5′-H, 2 × 4′-H), 7.57–7.55 (m, 2 H, 2 × 6′-H), 7.26–7.24 (m, 2 H, 2 × 7′-H), 6.12 (s, 2 H, 2 × 1-H), 4.66–4.60 (m, 2 H, 2 × C-1′-OC*H*$(CH_3)_2$), 4.38–4.36 (m, 2 H, C-8′-OC*H*$(CH_3)_2$), 2.65 (s, 6 H, 2 × Ar-CH_3), 2.40–2.32 (m, 2 H, 2 × 4-H), 1.43–1.33 (m, 28 H, 2 × 6-H_2, 2 × C-1′-OCH(C*H*$_3)_2$, 2 × C-8′-OCH(C*H*$_3)_2$), 1.10–1.08 (m, 6 H, 2 × 5-H_3), 0.91–0.88 (m, 6 H, 2 × 7-H_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.55, 183.39, 157.42, 154.56, 143.72, 140.31, 135.10, 133.51, 133.29, 127.04, 126.13, 124.60, 121.95, 119.21, 91.03, 79.42, 79.35, 72.71, 58.71, 29.61, 27.61, 22.41, 22.21, 22.06, 20.43, 20.41, 20.30, 20.29, 11.72 ppm. IR (KBr): $\tilde{\nu}$ = 2970, 1674, 1584, 1462, 1383 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 223.0 (4.478), 260.5 (4.371), 376.0 (3.709). HRMS (ESI): calcd. for $C_{28}H_{32}O_5$ + H^+: 449.23225; found: 449.23217.

Compound 2: To a stirred solution of IBX (112 mg, 0.40 mmol) in DMSO (0.5 mL) was added a solution of compound **10** (134 mg, 0.30 mmol) in CH_2Cl_2 (2 mL). The mixture was stirred at room temp. for 4 h and quenched by addition of an aqueous saturated $Na_2S_2O_3$ solution. The aqueous layer was extracted with CH_2Cl_2 and the organic layer washed with aqueous saturated $NaHCO_3$ solution, water, brine, dried with Na_2SO_4 and the solvent was evaporated under reduced pressure. The obtained crude product was purified by chromatography on silica gel using 10% EtOAc/pentane as the eluent to yield compound **2** (124 mg, 96%) as a viscous oil. $[\alpha]_D^{20}$ = +5.3 (c = 0.7, $CHCl_3$). ^1H NMR (600 MHz, $CDCl_3$): δ =

7.78–7.76 (m, 2 H, 5′-H, 4′-H), 7.57 (t, J = 8.4 Hz, 1 H, 6′-H), 7.27 (d, J = 8.4 Hz, 1 H, 7′-H), 4.65–4.59 (m, 1 H, C-1′-OCH(CH_3)$_2$), 4.41–4.34 (m, 1 H, C-8′-OCH(CH_3)$_2$), 2.59–2.53 (m, 1 H, 4-H), 2.37 (s, 3 H, Ar-CH_3), 1.54–1.49 (m, 2 H, 6-H_2), 1.41 (d, J = 6.0 Hz, 6 H, C-1′-OCH(CH_3)$_2$), 1.27 (d, J = 6.0 Hz, 6 H, C-8′-OCH-(CH_3)$_2$), 1.19 (d, J = 6.6 Hz, 3 H, 5-H_3), 0.97 (t, J = 7.2 Hz, 3 H, 7-H_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 183.44, 182.57, 181.54, 157.62, 155.0, 142.13, 140.92, 134.99, 134.48, 133.62, 127.0, 125.86, 123.69, 122.11, 119.27, 102.45, 82.28, 79.13, 72.76, 28.95, 28.06, 22.14, 22.03, 19.49, 19.30, 11.66 ppm. IR (KBr): $\tilde{\nu}$ = 2975, 2932, 2205, 1584, 1440 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 223.0 (4.513), 259.0 (4.389), 382.0 nm (3.777). HRMS (ESI): calcd. for $C_{28}H_{30}O_5$ + H^+: 447.21660; found: 447.21680.

Compound (*S*)-1: To a stirred solution of compound **2** (89 mg, 2.0 mmol) in AcOH (3.0 mL) was added H_2SO_4 (0.01 mL) at room temp. and stirring was continued at 60 °C for 1.5 h. The mixture was diluted with CH_2Cl_2 (30 mL) and the organic layer washed with water and brine. After drying over Na_2SO_4 and evaporation of the solvent under reduced pressure the crude product was purified by chromatography on silica gel using 20% EtOAc/pentane as the eluent to yield compound (*S*)-**1** (57 mg, 81% yield as a yellow solid. M.p. 209 °C. $[a]_D^{20}$ = +4.8 (c 0.3, DMSO). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.01 (s, 1 H, 6-H), 7.78 (dd, J = 8.2, 1.2 Hz, 1 H, 8-H), 7.64 (t, J = 8.2 Hz, 1 H, 9-H), 7.32 (dd, J = 8.2, 1.2 Hz, 1 H, 10-H), 6.23 (s, 1 H, 3-H), 2.98 (s, 3 H, Ar-CH_3), 2.76–2.64 (m, 1 H, 14-H), 2.02–1.88 (m, 1 H, 16-H_a), 1.82–1.68 (m, 1 H, 16-H_b), 1.41 (d, J = 6.8 Hz, 3 H, 15-H_3), 0.96 (t, J = 7.4 Hz, 3 H, 17-H_3) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 187.20, 182.01, 179.30, 172.88, 162.53, 156.73, 149.65, 136.23, 135.87, 132.23, 126.50, 125.43, 125.26, 119.78, 119.24, 116.81, 111.28, 40.43, 27.30, 24.22, 17.84, 11.71 ppm. IR (KBr): $\tilde{\nu}$ = 3377, 2923, 1655, 1459, 1317, 1222, 1075, 1031 cm^{-1}. UV (CH_3CN): λ_{max} (lg ε) = 239.0 (4.372), 267.0 (4.046), 416.5 nm (3.624). HRMS (ESI): calcd. for $C_{22}H_{18}O_5$ + H^+: 363.12270; found: 363.12261.

Isolation of Natural SS 43405-e for Comparison: The marine-derived streptomycete isolate B5543 was incubated for 72 h at 28 °C in a 20 L fermentor (18 L of M_2^+ medium).[11] After filtration, the filtrate and the mycelium were both extracted with ethyl acetate and the extracts were combined and evaporated under reduced pressure to afford 1.60 g of a brown crude residue. Flash chromatography of the residue on silica gel (30 × 500 mm) with a CH_2Cl_2/MeOH gradient afforded a yellow fraction I (317 mg), an orange-red fraction II (520 mg), and a brown fraction III (357 mg). Repeated PTLC of fraction I (5 plates 20 × 20 cm, cyclohexane/ethyl acetate, 70:30) yielded SS 3405e as a yellow solid (R_f = 0.85, 10.3 mg).

The spectroscopic data were identical in all respects with those of the synthetic material (*S*)-**1** except for the $[a]_D^{20}$ value with opposite sign: $[a]_D^{20}$ = +5.2 (c = 0.4, DMSO).

Acknowledgments

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