A New Route for the Total Synthesis of 6,7-Dihydroeponemycin

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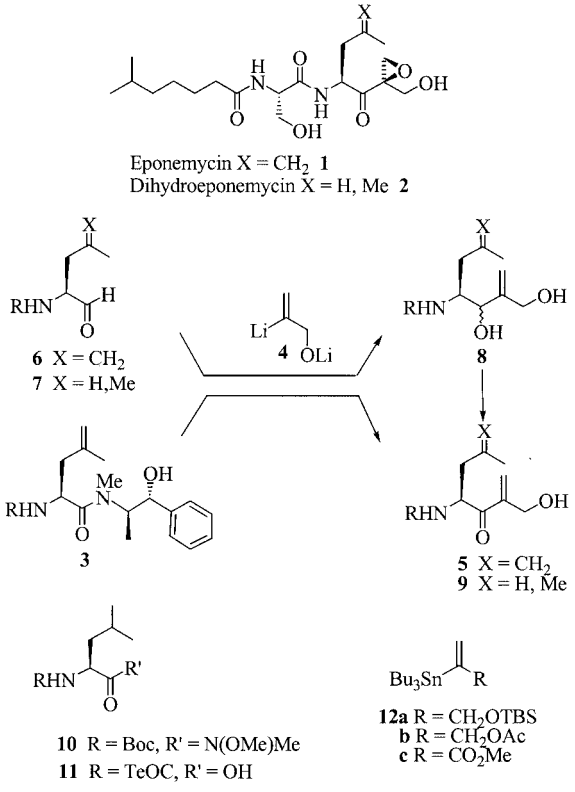
A new synthesis of dihydroeponemycin (**2**), a peptide epoxide with potent cytotoxic and antiangiogenesis activity, has been developed. In the initial steps, Fmoc-Leu-Cl was converted into the key amino ketone intermediate **9** by Stille coupling with tributylvinyltin, conjugate addition of $PhSAlMe_2$ to the derived enone, *S*-oxidation, and heat-induced *syn* elimination. Subsequent reaction of **9** with H_2O_2 and catalytic Triton B produced the corresponding epoxides as a 1:1 diastereomeric mixture in 89 % yield. These epoxides were separated and individually converted into **2** and(2*S*)-*epi*-dihydroeponemycin (**24**) in a four-step "one-pot" protocol (77 % overall yield in both cases).

Introduction

Eponemycin (**1**) has been shown by Crews et al. to be a potent inhibitor of the proteasome 20S.[1,2] The mode of action may be related to the interesting antiangiogenesis properties displayed by this molecule.[3−6] In the preceding paper[7] the synthesis of two new furan analogues of eponemycin was described, wherein methodology developed by Myers and co-workers[8−15] was employed for both the preparation of the didehydroleucine derivative **3** (R = Boc) and its subsequent reaction with 2-furyllithium. As an extension of this approach we envisaged that by reaction of amide **3** with the organolithium reagent **4** the key amino ketone intermediate **5** would be obtained (Scheme 1). Epoxidation of the enone double bond in **5** would complete construction of the reactive α′,β′-epoxy ketone motif present in **1**, thereby opening the way to the synthesis of this interesting molecule for further investigation of its biological activity.

Results and Discussion

The reaction of reagent **4** with the corresponding aminoaldehydes **6** and **7** was a pivotal step in several earlier approaches to eponemycin and its dihydro derivative **2** (which has the same potency as **1**).[16−18] This route provides a seemingly direct means to obtain the α-hydroxymethyl-substituted enone **5** and the corresponding saturated compound **9**. However, in addition to the preparation of the sensitive aminoaldehyde starting material, additional operations involving protection and deprotection of the primary OH group are required in this strategy in order to permit selective oxidation of the secondary alcohol function in **8**.



Scheme 1

Interestingly, the reactivity of dilithio reagent **4** towards acids and acid derivatives has received little attention.[19] In model experiments to explore the conversion of **3** to **5** the Weinreb-type amide derivative **10** [Boc-Leu-N(OMe)Me]

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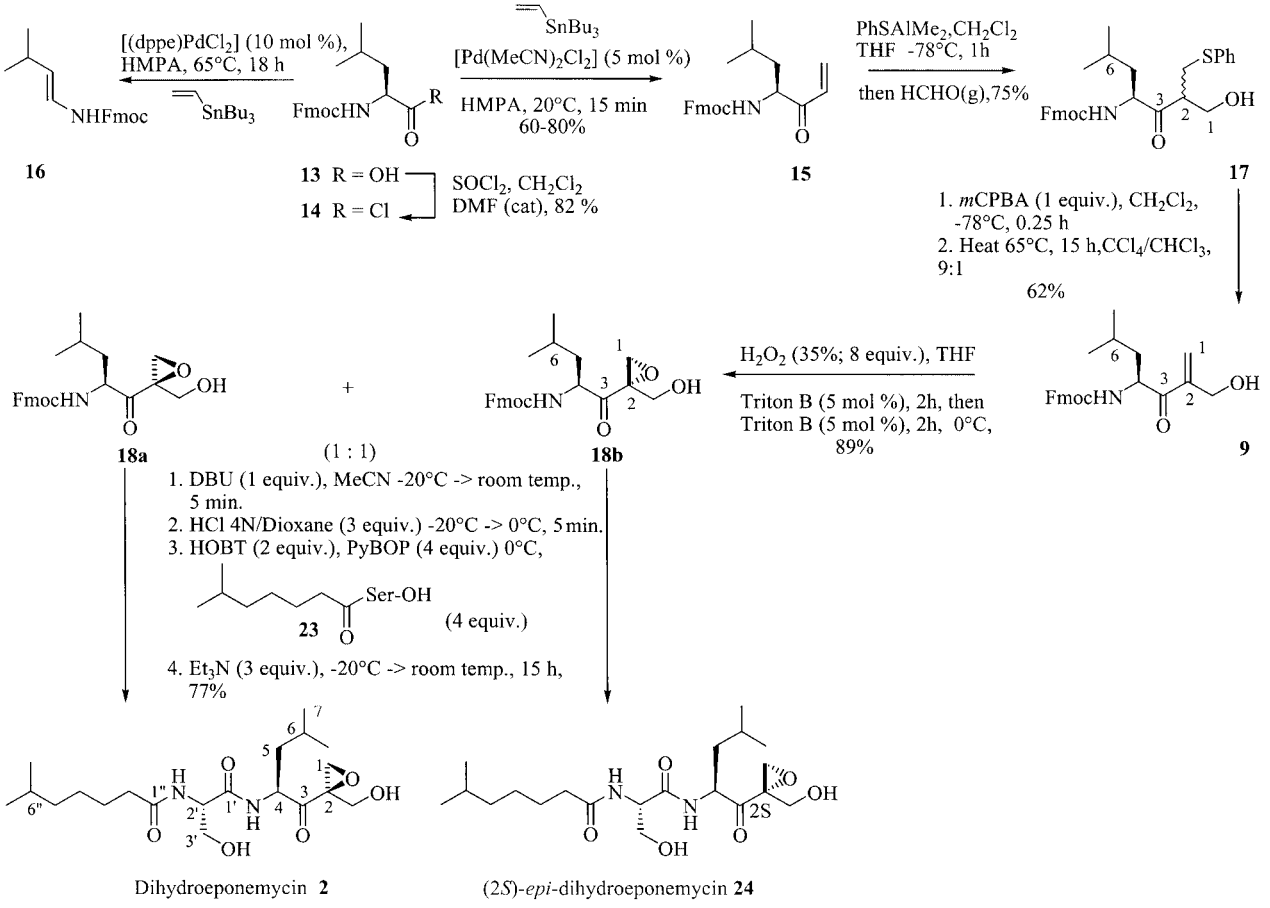
was treated with **4** under a variety of conditions. Despite a precedent for the reaction of the related Boc-leucine derivative with 2-propenyllithium,[20−22] the desired transformation was not achieved. Similarly, formation of **5** could not be detected in the reaction with TeOC-leucine **11** itself. Schmidt et al. have previously reported that the reaction of **4** with acid chlorides leads to competing allyl ester formation.[15]

As an alternative goal, the Pd^0-catalyzed Stille coupling[23,24] of the corresponding vinyltin reagents **12a**,**b**[25,26] and their ester precursor **12c**[25] with Fmoc-Leu-Cl **14** (obtained in 82 % yield from **13** and recrystallized from CH_2Cl_2/hexane) was subsequently evaluated as a means to synthesize dihydroeponemycin **2**. These reactions, conducted using 5−10 mol % $[Pd(PPh_3)_4]$ or $[Pd(PPh_3)_2BnCl$](with or without CuI) in a variety of solvents and temperatures up to 65 °C, either did not proceed, or resulted in degradation and formation of homocoupling products. In contrast, the reaction of **14** with *n*-tributylvinyltin in HMPA using catalytic $[Pd(MeCN)_2Cl_2]$ (5 mol %) was complete after 15 min at room temperature, providing enone **15** in 60−80 % isolated yield and with 98 % *ee* (Scheme 2). Most remarkable was the observation that at 65 °C the competing decarbonylation reaction occurred, leading to formation of **16** predominantly.[27]

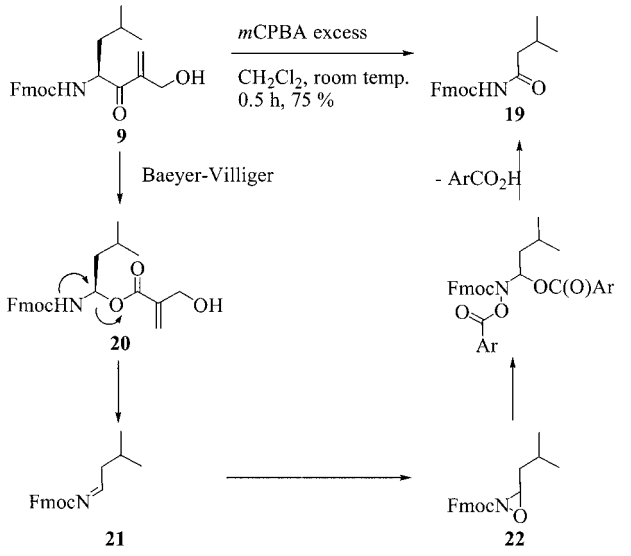
With this positive result in hand, the synthesis of dihydroeponemycin (**2**) became dependent upon finding suitable conditions to introduce the α-hydroxymethyl side chain present in **9**. The Baylis Hillman reaction[28] using formaldehyde is the obvious choice for this transformation. However, the general conditions, where an amine nucleophile (DABCO, DBU, etc.) is involved in the initial Michael addition step, are incompatible with the presence of the *N*-Fmoc group in **15**. Yamada et al. have recently described alternative conditions using a combination of tributylphosphane and (±)-1,1′-bi-2-naphthol combination,[29] but even with this mild Lewis base *N*-Fmoc deprotection occurred. In contrast, Me_2AlSPh proved to be a highly effective nucleophile and weak base for this process.[30,31] In the experiment, **15** was treated with Me_2AlSPh at −78 °C in CH_2Cl_2. THF was then added at the same temperature, followed by gaseous HCHO. Compound **17** was isolated as a white crystalline solid in 75 % yield. This intermediate was then converted into enone **9** in 62 % overall yield and greater than 97 % *ee* by *S*-oxidation (*m*CPBA, −78 °C, 15 min), and heating of the resulting sulfoxide in a 9:1 $CCl_4/CHCl_3$ mixture for 15 h.[32]

In the subsequent epoxidation step, it was again considered necessary to take precautions to avoid basic conditions that would result in unwanted Fmoc deprotection.



Scheme 2

This led us to attempt epoxidation of the deactivated double bond in **9** using excess *m*CPBA. In this reaction compound **19** was produced in 75 % yield (Scheme 3). A possible mechanism for the formation of this unexpected product involves an initial Baeyer−Villiger reaction giving **20**. This intermediate would be prone to elimination, giving the acylimine **21**, which would react readily with the peracid to give the oxaziridine **22**. The subsequent transformation of this oxaziridine to the amide **19** on treatment with *m*CPBA is a known process.[33]



Scheme 3

Ultimately, it was found that **9** could be converted into a 1:1 diastereomeric mixture of epoxides **18a,b** in high yield (89 %) by addition of a catalytic amount of Triton B (2 × 5 mol %) to a solution of **9** and H_2O_2 (in THF) at 0 °C.[34,35] These conditions, where the concentration of base present in the medium is kept very low, did not promote cleavage of the Fmoc group. Unfortunately, no asymmetric induction was observed when a Julia−Colonna-type process[36−38] was attempted by adding poly-L-leucine to the reaction medium. The diastereomeric epoxides **18a** and **18b** were readily separated by silica-gel column chromatography (EtOAc/cyclohexane, 1:9 to 3:7) and completely characterized.

The final step of the synthesis of dihydroeponemycin (**2**) involved the coupling with *N*-isooctanoyl-L-serine (**23**).[7] As feared, Fmoc deprotection by treatment of **18a** with Et_3N, DBU or Hunigs base was followed by instantaneous opening of the epoxide ring by the liberated amine. A subsequent (and unsuccessful) attempt was made to intercept the liberated amine before the intramolecular ring-opening/ring-forming process could occur, by ensuring that the activated acid component [PyBOP, HOBT] was present in the reaction medium at the moment when the amine base was added. Therefore, to avoid this problem, a practical four-step "one-pot" coupling protocol was developed, giving access to dihydroeponemycin **2** in 77 % yield, and in enantiomerically pure form. This involved adding DBU to a cooled (−20 °C) solution of **18a** in CH_3CN, warming the mixture to room temperature over five minutes, followed by recooling and "neutralizing" the liberated amine as its hydrochloride salt. PyBOP, HOBT and acid **23** were then added to the medium at 0 °C, and finally triethylamine was added dropwise at −20 °C. In an identical fashion the diastereomeric epoxide **18b** was coupled with acid **23** to give (2*S*)-*epi*-dihydroeponemycin (**24**) in 77 % overall yield. The ^1H and ^{13}C NMR spectroscopic data for our sample of synthetic dihydroeponemycin were identical in all respects with the values reported by Sugawara et al.[39,40]

Experimental Section

General Remarks: Unless otherwise stated, all reactions were carried out under argon with dry, freshly distilled solvents, flame-dried glassware, and magnetic stirring. All solvents were reagent grade. Diethyl ether and tetrahydrofuran (THF) were distilled from sodium/benzophenone under argon. Acetonitrile and dichloromethane (CH_2Cl_2) were distilled from calcium hydride. Triethylamine was distilled from calcium hydride and stored over potassium hydroxide. *N*,*N*-dimethylformamide (DMF) was purchased from Aldrich and used without purification unless otherwise noted. All reactions were monitored by thin layer chromatography (TLC) using E. Merk $60F_{254}$ precoated silica gel plates. Flash column chromatography was performed with the indicated solvents and using E. Merk silica gel 60 (particle size 0.035−0.070 mm unless otherwise stated). Yields refer to chromatographically and spectroscopically pure compounds, except where indicated otherwise. Melting points were taken on a Kofler melting point apparatus and are uncorrected. Optical rotations were measured on a Perkin−Elmer 341 polarimeter at the sodium D line (589 nm) and are reported as follows: $[\alpha]_D^{20}$ (*c* in g/100 mL, solvent). Infra-red spectra were recorded with a Perkin−Elmer 1710FT spectrophotometer. ^1H NMR spectra were recorded with a Bruker AC-200 (200 MHz) or with a Bruker AC-300 (300 MHz) spectrometer at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to residual chloroform (δ = 7.24 ppm) or residual methanol (δ = 4.78 ppm). ^{13}C NMR spectra were recorded with either a Bruker AC-200 (50 MHz) spectrometer or a Bruker AC-300 (75 MHz) spectrometer at ambient temperature using an internal deuterium lock. Chemical shifts are referenced to chloroform (δ = 77.0 ppm) or methanol (δ = 49.0 ppm). High and low resolution mass spectra were carried out by the I.C.M.O. Mass Spectrometry Service at the University of Paris XI. Microanalyses were performed by the I.C.S.N.-C.N.R.S. Elemental Analysis Center at Gif-sur-Yvette. High-performance liquid chromatography (HPLC) was performed with a Waters component Analytical system by the I.C.S.N.-C.N.R.S. HPLC Center at Gif-sur-Yvette.

Fmoc-Leu-Cl (14): DMF (54.5 μL, 0.71 mmol) and freshly distilled thionyl chloride (10.26 mL, 141.5 mmol) were added to a suspension of Fmoc-Leu-OH (5.00 g, 14.15 mmol) in CH_2Cl_2 (27 mL). The mixture was heated at reflux for 1.5 h, cooled to room temperature and the solvents evaporated to dryness under reduced pressure to afford the corresponding acid chloride as a colorless oil. Crystallization from CH_2Cl_2/hexane (1:10, 88 mL) afforded **14** (4.3 g, 82 %) as white crystals, which can be stored for months over P_4O_{10}. M.p. 82−83 °C. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 7.57 (d, ^3J = 7.3 Hz, 2 H, H_{Fmoc}), 7.39 (m, 2 H, H_{Fmoc}), 7.29 (m, 2 H, H_{Fmoc}), 5.16 (d, $^3J_{NH,2}$ = 7.8 Hz,

1 H, NH), 4.50 (m, 3 H, CH_{2Fmoc} and 2-H), 4.21 (t, ^3J = 6.6 Hz, 1 H, CH_{Fmoc}), 1.72 (m, 2 H, 3-H), 1.57 (m, 1 H, 4-H), 0.96 (m, 6 H, CH_3CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 176.11 (C-1), 156.41 (CO_{Fmoc}), [144.15 + 142.01 + 128.47 + 127.78 + 125.61 + 120.71, (C_{Fmoc})], 67.92 (CH_{2Fmoc}), 62.14 (2-C), 47.80(CH_{Fmoc}), 40.58 (C-3), [23.50 + 25.49, (C-5 and C-6)], 22.04 (C-4) ppm.

(4*S*)-4-(9-Fluorenylmethoxycarbonyl)amino-6-methylhept-1-en-3-one (15): Tributylvinyltin (2.60 g, 7.90 mmol) and bis(acetonitrile)palladium(II) chloride (98.6 mg, 0.38 mmol) were added to a vigorously stirred solution of acid chloride **14** (2.80 g, 7.53 mmol) in HMPT (22 mL). After 15 min at room temperature, the resulting black slurry was diluted with saturated aqueous KF (40 mL) and stirred for 24 h. The mixture was then poured into water (100 mL) and extracted twice with diethyl ether (50 mL). The combined organic phases were washed with brine, dried with Na_2SO_4, filtered through a short pad of Celite® and concentrated. Gradient flash column chromatography (SiO_2, EtOAc/cyclohexane, 7:93, EtOAc/cyclohexane, 8:92) afforded **15** (1.70 g, 63 %) as a soft white solid. $[\alpha]_D^{20}$ = + 29.5 (*c* = 1.2, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, ^3J = 7.5 Hz, 2 H, H_{Fmoc}), 7.58 (dd, ^3J = 7.1 Hz, ^4J = 2.5 Hz, 2 H, H_{Fmoc}), 7.38 (t, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 7.29 (t, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 6.41 (m, 2 H, 1-H^a and 2-H), 5.89 (dd, $^2J_{1b,1a}$ = 2.2 Hz, 1 H, $^3J_{1b,2}$ = 9.2 Hz, 1-H^b), 5.38 (d, ^3J = 8.3 Hz, 1 H, NH), 4.72 (m, 1 H, 4-H), 4.38 (d, ^3J = 7.0 Hz, 2 H, CH_{2Fmoc}), 4.20 (t, ^3J = 7.0 Hz, 1 H, CH_{Fmoc}), 1.60 (m, 3 H, 5-H and 6-H), 0.99 (d, ^3J = 6.4 Hz, 3 H, CH_3), 0.91 (d, ^3J = 6.7 Hz, 3 H, CH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 199.46 (C-3), 156.78 (CO_{Fmoc}), [144.45 + 142.00 + 128.37 + 127.75 + 125.78 + 120.64, (C_{Fmoc})], 133.89 (C-2), 130.89 (C-1), 67.6 (CH_{2Fmoc}), 56.85 (C-4), 47.91 (CH_{Fmoc}), 42.3 (C-5), 25.55 (C-6), [24.02 + 22.49, (C-7 and C-8)] ppm. MS (ES, Na): *m*/*z* = 386.2 [M + Na]$^+$, 749.4 [2M + Na]$^+$, 750.4 [2M + H + Na]$^+$. HRMS (ES, Na): *m*/*z* = 386.17321 [M + Na]$^+$, calcd. for $C_{23}H_{25}NO_3Na$: *m*/*z* = 386.17321. $C_{23}H_{25}NO_3$ (363.46): calcd. C 76.01, H 6.93, N 3.85, O 13.21; found C 76.01, H 6.88, N 3.58, O 13.25. Chiral HPLC (Analytical column, Chiralpak® AD; mobile phase: 60:40 hexane/ethanol; flow rate = 1 mL/min; detection wavelength: 212 nm; room temperature; retention time = 6.95 min): *ee* ≥ 98 %.

1-(9-Fluorenylmethoxycarbonyl)amino-3-methylbut-1-ene (16) (decarbonylated product): ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, ^3J = 7.3 Hz, 2 H, H_{Fmoc}), 7.56 (d, ^3J = 7.3 Hz, 2 H, H_{Fmoc}), 7.39 (m, 2 H, H_{Fmoc}), 7.32 (m, 2 H, H_{Fmoc}), 6.41 (dd, $^3J_{1,NH}$ = 9.5 Hz, $^3J_{1,2}$ = 14.0 Hz, 1 H, 1-H), 6.24 (d, $^3J_{NH,1}$ = 9.5 Hz, 1 H, NH), 4.99 (dd, $^3J_{2,3}$ = 6.9 Hz, $^3J_{2,1}$ = 14.0 Hz, 1 H, 2-H), 4.43 (d, $^3J_{2',3'}$ = 6.8 Hz, 2 H, CH_{2Fmoc}), 4.20 (t, ^3J = 6.8 Hz, 1 H, CH_{Fmoc}), 2.28 (m, 1 H, 3-H), 0.98 (m, 6 H, CH_3CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 154.30 (CO_{Fmoc}), [144.41 + 141.98 + 128.41 + 127.74 + 125.64 + 120.68 (C_{Fmoc})] , 121.96 (C-1), 119.35 (C-2), 67.57 (CH_{2Fmoc}), 47.76 (CH_{Fmoc}), 30.84 (C-3), 23.59 (CH_3CHCH_3) ppm. MS (ES, Na): *m*/*z* = 637.3 [2M + Na]$^+$, 330.2 [M + Na]$^+$. HRMS (ES, Na): *m*/*z* = 330.14700 [M + Na]$^+$, calcd. for $C_{20}H_{21}NO_2Na$: *m*/*z* = 330.14700.

(4*S*)-4-(9-Fluorenylmethoxycarbonyl)amino-1-hydroxy-6-methyl-2-phenylthiomethylheptan-3-one (17): $AlMe_3$ (2 M in hexanes, 5.03 mL, 10.07 mmol) was slowly added to a vigorously stirred solution of thiophenol (1.05 mL, 10.07 mmol) in CH_2Cl_2 (10 mL) at 0 °C. After 1 h, the resulting mixture was cooled to −78 °C and treated with a solution of **15** (3.05 g, 8.39 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was then stirred at −78 °C for 1 h and diluted with THF (61 mL). Gaseous formaldehyde was bubbled through this solution until the starting material disappeared by TLC (approx.15 min). The resulting mixture was cautiously poured into a mixture of ice cold 1 M HCl and extracted with EtOAc (3 × 80 mL). The combined organic phases were washed with 1 M HCl and with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. Gradient flash column chromatography (SiO_2, EtOAc/cyclohexane, 15:85, EtOAc/cyclohexane, 1:4) afforded **17** as an oil which gave white crystals on standing (3.16 g, 75 %). M.p. 99 °C. $[\alpha]_D^{20}$ = +73.5 (*c* = 1.07, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.75 (d, ^3J = 7.5 Hz, 2 H, H_{Fmoc}), 7.57 (dd, ^3J = 7.0 Hz, ^4J = 3.9 Hz, 2 H, H_{Fmoc}), 7.39 (m, 4 H, H_{Fmoc}), 7.29 (m, 4 H, H_{SPh}), 7.17 (m, 1 H, H_{SPh}), 5.13 (d, ^3J = 8.5 Hz, 1 H, NH), 4.43 (m, 1 H, 4-H), 4.39 (d, ^3J = 6.9 Hz, 2 H, CH_{2Fmoc}), 4.19 (t, ^3J = 6.9 Hz, 1 H, CH_{Fmoc}), 3.87 (m, 2 H, 1-H), 3.27 (dd, $^3J_{SCH_2{}^a,2}$ = 4.8 Hz, $^2J_{SCH_2{}^a,SCH_2{}^b}$ = 12.5 Hz, 1 H, CH_2^a−S), 3.00 (m, 2 H, CH_2^b−S and 2-H), 2.27 (s, 1 H, OH), 1.64 (m, 1 H, 6-H), 1.48 (ddd, ^3J = 3.2 Hz, ^3J = 4.0 Hz, $^2J_{5a,5b}$ = 9.8 Hz, 1 H, 5-H^a), 1.23 (m, 1 H, 5-H^b), 0.86 (m, 6 H, CH_3CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 212.24 (C-3), 156.91 (CO_{Fmoc}), [144.36 + 142.01 + 128.40 + 125.75 + 120.67 + 127.74, (C_{Fmoc})], 135.56 (C_{PhS}), 130.85 (C_{PhS}), 129.89 (C_{PhS}), 127.51 (C_{PhS}), 67.59 (CH_{2Fmoc}), 62.76 (C-1), 58.50 (C-4), 50.49 (C-2), 47.87(CH_{Fmoc}), 40.21 (C-5), 32.73 (CH_2-S), 25.51 (C-6), [23.95 + 21.98, (CH_3−CH−CH_3)] ppm. MS (ES, Na): *m*/*z* = 526.2 [M + Na]$^+$, 542.2 [M + K]$^+$. HRMS (ES, Na): *m*/*z* = 526.20280 [M + Na]$^+$, calcd. for $C_{30}H_{33}NSO_4Na$: *m*/*z* = 526.20280. $C_{30}H_{33}NO_4S$ (503.66): calcd. C 71.54, H 6.60, N 2.78, O 12.71, S 6.37; found C 71.39, H 6.71, N 2.60, O 12.57, S 6.28.

(4*S*)-4-(9-Fluorenylmethoxycarbonyl)amino-2-hydroxymethyl-6-methylhept-1-en-3-one (9): A solution of *m*CPBA (70 %, 1.40 g, 5.66 mmol) in CH_2Cl_2 (12 mL) was added to a stirred solution of **17** (2.85 g, 5.66 mmol) in CH_2Cl_2 (90 mL) at −78 °C. After 15 min, the reaction mixture was warmed to room temperature, quenched with 10 % aqueous Na_2SO_3 (100 mL) and extracted twice with diethyl ether (40 mL). The combined organic layers were washed twice with saturated aqueous $NaHCO_3$, with brine, dried with Na_2SO_4, filtered and concentrated in vacuo to provide the corresponding unstable sulfoxide (3.00 g, 80 %) as a colorless oil that was used without any further purification.

The above sulfoxide in solution in $CCl_4/CHCl_3$ (9:1, 300 mL) was heated to reflux at 65 °C for 15 h. The resulting solution was cooled to room temperature and the solvents evaporated. Gradient flash column chromatography (SiO_2, EtOAc/cyclohexane, 1:4, EtOAc/cyclohexane, 1:3, EtOAc/cyclohexane, 2:3) afforded **9** (1.38 g, 62 % over two steps) as a light pink glassy solid. $[\alpha]_D^{20}$ = +39.7 (*c* = 1.05, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, ^3J = 7.5 Hz, 2 H, H_{Fmoc}), 7.57 (dd, ^3J = 7.2 Hz, ^4J = 2.0 Hz, 2 H, H_{Fmoc}), 7.38 (t, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 7.29 (td, ^3J = 7.4 Hz, ^4J = 1.1 Hz, 2 H, H_{Fmoc}), 6.22 (s, 1 H, 1-H^a), 6.13 (s, 1 H, 1-H^b), 5.37 (d, ^3J = 8.8 Hz, 1 H, NH), 5.10 (m, 1 H, 4-H), 4.36 (m, 4 H, CH_{2Fmoc} + 9-H), 4.20 (t, ^3J = 7.0 Hz, 1 H, CH_{Fmoc}), 2.11 (s, 1 H, OH), 1.71 (m, 1 H, 6-H), 1.52 (m, 1 H, 5-H^a), 1.38 (m, 1 H, 5-H^b), 1.00 (d, $^3J_{7,6}$ = 6.5 Hz, 3 H, CH_3CHCH_3), 0.90 (d, $^3J_{7,6}$ = 6.6 Hz, 3 H, CH_3CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 201.96 (C-3), 157.76 (CO_{Fmoc}), 145.53 (C-2), [144.40 + 141.99 + 128.38 + 127.74 + 125.75 + 120.65, (C_{Fmoc})], 127.14 (C-1), 67.63 (CH_{2Fmoc}), 62.99 (C-9), 54.10 (C-4), 47.90 (CH_{Fmoc}), 43.51 (C-5), 25.61 (C-6), [24.03 + 22.31, (C-7 and C-8)] ppm. MS (Electrospray): *m*/*z* = 416.1 [M + Na]$^+$. HRMS (ES, Na): *m*/*z* = 416.18378 [M + Na]$^+$, calcd. for $C_{24}H_{27}NO_4Na$: *m*/*z* = 416.18378. $C_{24}H_{27}NO_4$ (393.48): calcd. C 73.26, H 6.92, N 3.56, O 16.26; found C 72.99, H 7.11, N 3.46, O 16.34. Chiral HPLC (Analytical column, Chiralpak® AD; mobile phase: 60:40 hexane/ethanol; flow rate = 1 mL/min; detec-

tion wavelength: 212 nm; room temperature; retention time = 6.79 min): *ee* ≥ 97 %.

(2*RS*,4*S*)-4-(9-Fluorenylmethoxycarbonyl)amino-2-hydroxymethyl-6-methyl-1,2-oxiranylheptan-3-one (18): H_2O_2 (35 wt.-% in water, 1.09 mL, 12.4 mmol) and Triton B® (40 wt.-% in MeOH, 35 μL, 77.51 μmol) were added dropwise to a solution of **9** (610 mg, 1.55 mmol) in THF (1.8 mL) at 0 °C. After stirring at 0 °C for 2 h a second portion of Triton B® (40 wt.-% in MeOH, 35 μL, 77.51 μmol) was added in order to take the reaction to completion. The resulting mixture was cautiously quenched with saturated aqueous NH_4Cl (10 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were dried with Na_2SO_4, filtered and concentrated in vacuo to afford a 1:1 mixture of epoxides **18a** and **18b** which were easily separated by gradient flash column chromatography (SiO_2, EtOAc/cyclohexane,1:9, EtOAc/cyclohexane, 1:4, EtOAc/cyclohexane, 3:7): (**18a**: 270 mg, **18b**: 218 mg, mixed fractions: 80 mg, total yield 89 %). **18a:** light pink oil. $[\alpha]_D^{20}$ = +61.5 (*c* = 1.03, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 7.56 (m, 2 H, H_{Fmoc}), 7.38 (t, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 7.29 (t, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 5.07 (d, ^3J = 8.6 Hz, 1 H, NH), 4.39 (m, 1 H, 4-H), 4.34 (d, ^3J = 7.3 Hz, 2 H, CH_{2Fmoc}), 4.18 (m, 2 H, 9-H^a and CH_{Fmoc}), 3.77 (dd, $^3J_{9b,OH}$ = 7.2 Hz, $^2J_{9b,9a}$ = 12.6 Hz, 1 H, 9-H^b), 3.29 (d, $^2J_{1a,1b}$ = 4.8 Hz, 1 H, 1-H^a), 3.08 (d, $^2J_{1b,1a}$ = 4.8 Hz, 1 H, 1-H^b), 1.84 (t, ^3J = 7.2 Hz, 1 H, OH), 1.71 (m, 1 H, 6-H), 1.56 (m, 1 H, 5-H^a), 1.23 (m, 1 H, 5-H^b), 0.95 (m, 6 H, CH_3CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 209.33 (C-3), 156.89 (CO_{Fmoc}), [144.34 + 141.99 + 128.42 + 127.76 + 125.75 + 120.69, (C_{Fmoc})], 67.68 (CH_{2Fmoc}), 62.50 (C-2), 62.04 (C-9), 52.91 (C-4), 49.82 (C-1), 47.83 (CH_{Fmoc}), 40.38 (C-5), 25.74 (C-6), [24.05 + 21.88, (*C*H$_3$CH*C*H$_3$)] ppm. **18b:** light yellow oil. $[\alpha]_D^{20}$ = −15.5 (*c* = 1.00, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.74 (d, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 7.56 (m, 2 H, H_{Fmoc}), 7.38 (t, ^3J = 7.3 Hz, 2 H, H_{Fmoc}), 7.30 (t, ^3J = 7.3 Hz, 2 H, H_{Fmoc}), 5.07 (d, ^3J = 7.6 Hz, 1 H, NH), 4.60 (m, 1 H, 4-H), 4.41 (d, ^3J = 6.5 Hz, 2 H, CH_{2Fmoc}), 4.19 (t, ^3J = 6.5 Hz, 1 H, CH_{Fmoc}), 4.10 (dd, $^3J_{CH_2^a,OH}$ = 5.4 Hz, $^2J_{CH_2^a,CH_2^b}$ = 12.6 Hz, 1 H, *CH*$_2^a$−OH), 3.76 (dd, $^3J_{CH_2^b,OH}$ = 8.0 Hz, $^2J_{CH_2^b,CH_2^a}$ = 12.6 Hz, 1 H, *CH*$_2^b$−OH), 3.04 (d, $^2J_{1a,1b}$ = 4.5 Hz, 1 H, 1-H^a), 2.96 (d, $^2J_{1b,1a}$ = 4.5 Hz, 1 H, 1-H^b), 2.25 (m, 1 H, OH), 1.66 (m, 1 H, 6-H), 1.37 (m, 2 H, 5-H), 0.95 (d, ^3J = 6.6 Hz, 3 H, CH_3CHCH$_3$), 0.92 (d, ^3J = 6.6 Hz, 3 H, CH$_3$CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.07 (C-3), 156.82 (CO_{Fmoc}), [144.37 + 142.03 + 128.42 + 127.76 + 125.67 + 120.68, (C_{Fmoc})], 67.67 (CH_{2Fmoc}), 62.87 (C-2 and *C*H$_2$OH), 54.82 (C-4), 50.37 (C-1), 47.88 (CH_{Fmoc}), 40.95 (C-5), 25.51 (C-6), [23.98 + 22.08, (*C*H$_3$CH*C*H$_3$)] ppm. MS (ES, Na$^+$): *m*/*z* = 432.1 [M + Na]$^+$, 448.1 [M + K]$^+$. HRMS (ES, Na): *m*/*z* = 432.17869 ([M + Na]$^+$, calcd. for $C_{24}H_{27}NO_5Na$: *m*/*z* = 432.17869. $C_{24}H_{27}NO_5$ (409.48): calcd. C 70.40, H 6.65, N 3.42, O 19.54; found C 70.69, H 6.35, N 3.18, O 19.44.

***N*-(9-Fluorenylmethoxycarbonyl)3-methylbutyramide (19):** *m*CPBA (70 %, 62.65 mg, 0.25 mmol) was added to a stirred solution of **9** (50 mg, 0.13 mmol) in CH_2Cl_2 (0.25 mL) at room temperature. After 15 min, the resulting reaction mixture was quenched with a 10 % aqueous Na_2SO_3 (1.5 mL) and extracted with diethyl ether (3 × 0.5 mL). The combined organic phases were washed twice with saturated $NaHCO_3$ and with brine, dried with Na_2SO_4, filtered and concentrated. Gradient flash column chromatography (SiO_2, EtOAc/cyclohexane, 1:4, EtOAc/cyclohexane, 2:3) afforded **19** (31 mg, 75 %) as a crystalline solid. M.p. 159 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.93 (s, 1 H, NH), 7.75 (d, ^3J = 7.5 Hz, 2 H, H_{Fmoc}), 7.58 (d, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 7.40 (t, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 7.30 (t, ^3J = 7.4 Hz, 2 H, H_{Fmoc}), 4.47 (d, ^3J = 6.8 Hz, 2 H, CH_{2Fmoc}), 4.23 (t, ^3J = 6.8 Hz, 1 H, CH_{Fmoc}), 2.61 (d, $^3J_{2,3}$ = 6.9 Hz, 2 H, 2-H), 2.16 (m, 1 H, 3-H), 0.97 (d, ^3J = 6.7 Hz, 6 H, CH_3CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 174.86 (C-1), [152.42 + 143.89 + 128.63 + 127.87 + 125.61 + 120.80, (C_{Fmoc})], 142.00 (C-4′), 68.37 (CH_{2Fmoc}), 47.38 (CH_{Fmoc}), 45.41 (C-2), 25.65 (C-3), 23.13 (C-4.5) ppm. MS (ES, Na): *m*/*z* = 346.2 [M + Na]$^+$, 362.1 [M + K]$^+$, 669.5 [2M + Na]$^+$. HRMS (ES, Na): *m*/*z* = 346.14191 [M + Na]$^+$, calcd. for $C_{20}H_{21}NO_3Na$: *m*/*z* = 346.14191.

(2*R*,4*S*)-2-Hydroxymethyl-6-methyl-4-[(*S*)-*N*-(6-methylheptanoyl)-seryl]amino-1,2-oxiranylheptan-3-one (6,7-Dihydroeponemycine) (2): DBU (37.3 μL, 0.24 mmol) was added dropwise to a solution of **18a** (100 mg, 0.24 mmol) in freshly distilled acetonitrile (1 mL) at −20 °C. The mixture was immediately warmed to room temperature for 5 min. The resulting dark purple solution was recooled to −20 °C and treated with HCl in 1,4-dioxane (4 M, 183 μL, 0.73 mmol). After 5 min at −20 °C, the vigorously stirred mixture was warmed to 0 °C and diluted with freshly distilled acetonitrile (4 mL) before the successive addition of HOBt (66 mg, 0.49 mmol), PyBOP (513.5 mg, 0.98 mmol) and acid **7** (225.9 mg, 0.98 mmol). The resulting mixture was recooled to −20 °C and treated with triethylamine (103 μL, 0.73 mmol). After stirring for 5 min at −20 °C, the solution was warmed to 0 °C for 1 h and stirred at room temperature for 12 h . The mixture was diluted with diethyl ether (2 mL), cooled to 0 °C, quenched with brine (15 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were successively washed with saturated aqueous NH_4Cl, 2 % aqueous $KHSO_4$, saturated aqueous $NaHCO_3$ and brine, and then dried with Na_2SO_4, filtered and concentrated. Flash column chromatography (SiO_2:15 μm, CH_2Cl_2/MeOH 95:5) afforded **2** (75 mg, 77 %) as a colorless gum. $[\alpha]_D^{20}$ = +30.2 ($CHCl_3$, c= 1.00). IR ($CHCl_3$): $\tilde{\nu}$ = 3403, 3150, 2960, 1720, 1650, 1510, 1050 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 7.13 [d, ^3J = 7.1 Hz, 1 H, N*H*(C-4)], 6.50 [d, ^3J = 7.0 Hz, 1 H, N*H*(C-2′)], 4.49 (m, 2 H, 2′,4-H), 4.19 [d, $^2J_{C\text{-}2CH_2^a,C\text{-}2CH_2^b}$ = 12.6 Hz, 1 H, (C-2)CH_2^a], 4.00 (dd, $^2J_{3'a,3'b}$ = 11.4 Hz, $^3J_{3'a,2'}$ = 3.4 Hz, 1 H, 3′-H^a), 3.70 [d, $^2J_{9b,9a}$ = 12.6 Hz, 1 H, (C-2)CH_2^b], 3.55 (dd, $^2J_{3'b,3'a}$ = 11.4 Hz, $^3J_{3'b,2'}$ = 5.8 Hz, 1 H, 3′-H^b), 3.29 (d, $^2J_{1a,1b}$ = 4.9 Hz, 1 H, 1-H^a), 3.07 (d, $^2J_{1b,1a}$ = 4.9 Hz, 1 H, 1-H^b), 2.20 (s and t, 3 H, $^3J_{2'',3''}$ = 7.6 Hz, 2′′-H and OH), 1.62 (s, 1 H, OH), 1.57 (m, 4 H, 3′′-H^a, 5-H^a, 6-H and 6′′-H), 1.27 (m, 4 H, 4′′-H, 5-H^b and 3′′-H^b), 1.16 (m, 2 H, 5′′-H), 0.92 (d, $^3J_{7,6}$ = 6.2 Hz, 3 H, CH_3CHCH$_3$), 0.91 (d, 3 H, $^3J_{CH_3,6}$ = 6.1 Hz, CH$_3$CHCH_3), 0.83 (d, ^3J = 6.6 Hz, 6 H, CH_3CHCH_3) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 208.64 (C-3), 174.65 (C-1′′), 172.12 (C-1′), 63.43 (C-3′), 62.99 (C-2), 62.23 (C-9), 54.13 (C-2′), 52.55 (C-4), 50.08 (C-1), 39.25 (C-5 and C-5′′), 37.19 (C-2′′), 28.46 (C-6′′), 27.68 (C-4′′), 26.53 (C-3′′), 25.96 (C-6), 23.97 (C-8), 23.24 (C-7′′ and C-8′′), 21.74 (C-7) ppm. MS (ES, Na): *m*/*z* = 423.2 [M + Na]$^+$, 439.2 [M + K]$^+$. HRMS (ES, Na): *m*/*z* = 423.24711 [M + Na]$^+$, calcd. for $C_{20}H_{36}N_2O_6Na$: *m*/*z* = 423.24710. $C_{20}H_{36}N_2O_6$ (400.51): calcd. C 59.98, H 9.06, N 6.99; found C 60.31, H 9.19, N 6.66.

(2*S*,4*S*)-2-Hydroxymethyl-6-methyl-4-[(*S*)-*N*-(6-methylheptanoyl)-seryl]amino-1,2-oxiranylheptan-3-one (2-*epi*-Dihydroeponemycine) (24): DBU (22.4 μL, 0.15 mmol) was added dropwise to a solution of **14b** (60 mg, 0.15 mmol) in freshly distilled acetonitrile (600 μL) at −20 °C. The mixture was immediately warmed to room temperature for 5 min. The resulting dark purple solution was recooled to −20 °C and treated with a solution of HCl in 1,4-dioxane (4 M, 110 μL, 0.44 mmol). After 5 min at −20 °C, the vigorously stirred mixture was warmed to 0 °C and diluted with freshly distilled acetonitrile (2.4 mL) before the successive addition of HOBt

(39.6 mg, 0.29 mmol), PyBOP (308.1 mg, 0.59 mmol) and acid **7** (135.6 mg, 0.59 mmol). The resulting mixture was recooled to −20 °C and treated with triethylamine (61.6 μL, 0.44 mmol). After stirring for 5 min at −20 °C, the solution was warmed to 0 °C for 1 h and stirred for 12 h at room temperature. The mixture was diluted with diethyl ether (2 mL), cooled to 0 °C, quenched with brine (15 mL) and extracted with diethyl ether (3 × 5 mL). The combined organic layers were washed successively with saturated NH_4Cl, 2 % $KHSO_4$, saturated $NaHCO_3$ and brine, dried with Na_2SO_4, filtered and concentrated. Flash column chromatography [SiO_2 (15 μm), CH_2Cl_2/MeOH, 95:5] afforded **16** (45 mg, 77 %) as a white solid. $[\alpha]_D^{20} = -88.61$ ($CHCl_3$, c = 1.00). IR ($CHCl_3$): $\tilde{\nu}$ = 3390, 3150, 2950, 1720, 1640, 1520, 1060 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 7.31 [d, ^3J = 7.2 Hz, 1 H, N*H*(C-4)], 6.65 [d, ^3J = 6.9 Hz, 1 H, N*H*(C-2′)], 4.65 (m, 1 H, 4-H), 4.42 (m, 1 H, 2′-H), 4.22 (d, $^2J_{C\text{-}2CH_2{}^a,C\text{-}2CH_2{}^b}$ = 12.6 Hz, 1 H, 9-H^a), 4.11 (dd, $^2J_{3'a,3'b}$ = 11.6 Hz, $^3J_{3'a,2'}$ = 2.7 Hz, 1 H, 3′-H^a), 3.63 (d, $^2J_{C\text{-}2CH_2{}^b,C\text{-}2CH_2{}^a}$ = 12.6 Hz, 1 H, 9-H^b), 3.56 (dd, $^2J_{3'b,3'a}$ = 11.7 Hz, $^3J_{3'b,2'}$ = 6.5 Hz, 1 H, 3′-H^b), 3.03 (d, $^2J_{1a,1b}$ = 4.6 Hz, 1 H, 1-H^a), 2.96 (d, $^2J_{1b,1a}$ = 4.6 Hz, 1 H, 1-H^b), 2.22 (t, $^3J_{2'',3''}$ = 7.7 Hz, 2 H, 2′′-H), 1.51 (m, 3 H, 3′′-H^a, 6-H and 6′′-H), 1.43 (m, 2 H, 5-H), 1.28 (m, 3 H, 4′′-H and 3′′-H^b), 1.17 (m, 2 H, 5′′-H), 0.91 (d, $^3J_{7,6}$ = 6.5 Hz, 3 H, C*H*$_3$CHCH$_3$), 0.90 (d, $^3J_{CH_3,6}$ = 6.5 Hz, 3 H, CH$_3$CH*CH*$_3$), 0.84 (d, ^3J = 6.6 Hz, 6 H, C*H*$_3$CHC*H*$_3$) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 206.71 (C-3), 174.82 (C-1′′), 171.77 (C-1′), 63.63 (C-2), 63.48 (C-9), 63.32 (C-3′), 54.46 (C-2′), 53.12 (C-4), 50.22 (C-1), 39.58 (C-5), 39.25 (C-5′′), 37.17 (C2′′), 28.47 (C-6′′), 27.69 (C-4′′), 26.52 (C-3′′), 25.55 (C-6), 23.91 (C-8), 23.25 (*C*H$_3$CH*C*H$_3$), 22.19 (C-7) ppm. MS (ES, Na): *m/z* = 423.2 $[M + Na]^+$, 439.2 $[M + K]^+$. HRMS (ES, Na): *m/z* = 423.24711 $[M + Na]^+$, calcd. for $C_{20}H_{36}N_2O_6Na$: *m/z* = 423.24710. $C_{20}H_{36}N_2O_6$ (400.51): calcd. C 59.98, H 9.06, N 6.99; found C 60.21, H 9.17, N 6.86.

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