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The Knight route to cyclopiazonic acid: enantioselective synthesis of a key intermediate

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ABSTRACT

The indole alkaloid α-cyclopiazonic acid (CPA) is one of the few known inhibitors of sarco(endo) plasmic reticulum Ca^{2+}-ATPase (SERCA) besides thapsigargin and artemisinin. Inhibitors of SERCA hold promise as novel anticancer and antimalarial drugs. Since its structure elucidation three racemic syntheses of α-cyclopiazonic acid have been published. We report now the first enantioselective and high yielding synthesis of a key-intermediate of the Knight synthesis, currently the most efficient route to CPA. Our synthesis is based on a diastereoselective 1,4-cuprate addition followed by an enolate azidation of an indolylacrylic acid modified with the Evans auxiliary.

1. Introduction

The mycotoxins α-cyclopiazonic acid (CPA, **1**) and β-cyclopiazonic acid (**2**) have been isolated from the fungus *Penicillium cyclopium* Westling, which grows worldwide on stored grain and cereal products.[1] Toxicity and mode of action of α-cyclopiazonic acid, the major toxic principle of *P. cyclopium* have been studied thoroughly as a consequence of several poisonings after ingestion of contaminated grain products.[2,3] CPA (**1**) specifically inhibits a Ca^{2+}-ATPase of the sarcoendoplasmic reticulum (SERCA), which is essential for calcium reuptake in the muscle contraction–relaxation cycle.[4,5] Other inhibitors of SERCAs comprise the terpenoids thapsigargin and most interesting artemisinin, an antimalarial drug.[6,7] While thapsigargin and in particular α-cyclopiazonic acid show a remarkable toxicity against mammals, this was not found for artemisinin. Taken all these findings together SERCA inhibitors represent promising lead structures for the development of novel anticancer and antimalarial drugs (Fig. 1).

Since the structure elucidation of CPA in 1968 three racemic syntheses were published by Kozikowski[8] (1984), Natsume[9] (1985) and Knight[10] (2005), all starting from the indole ring system.

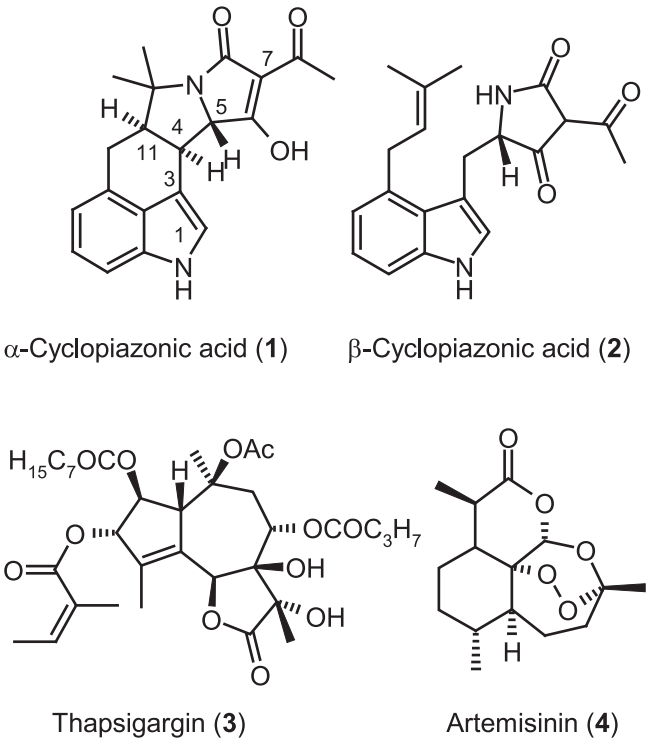

Figure 1. Known inhibitors of SERCA.

Abbreviations: DBU, 1,8-Diazabicyclo[5.4.0]undec-7-ene; DCM, Dichloromethane; DMF, Dimethylformamide; KHMDS, Potassium hexamethyldisilazide; Ns, *p*-Nosyl; TBDPS, *tert*-Butyl-diphenylsilyl; THF, Tetrahydrofurane; Ts, Tosyl.

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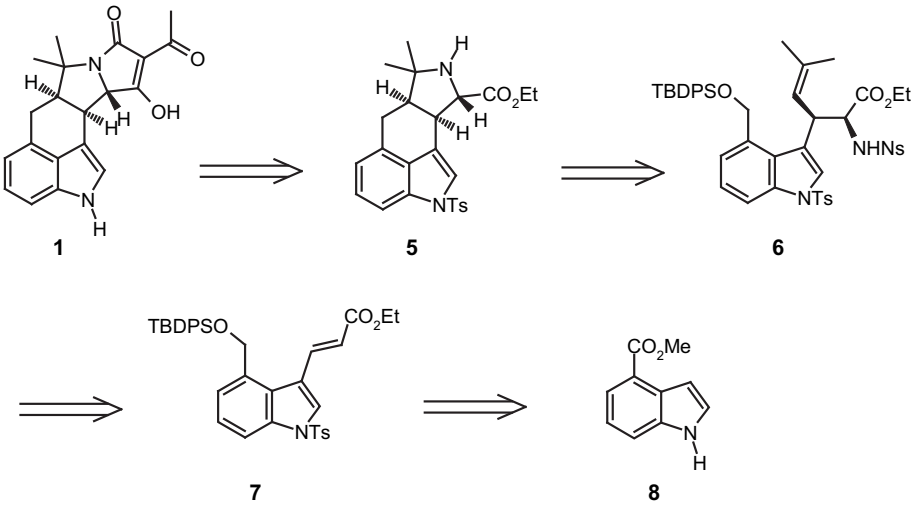
A biomimetic approach via β-cyclopiazonic (**2**) acid was detailed by Aggarwal[11] in 2007.

We wish to report here the first enantioselective synthesis of the tryptophan analogue **6**, a central precursor in the 'Knight synthesis' (Scheme 1), which currently represents the most efficient route to CPA (**1**). In particular, the tetracyclic scaffold **5** is established from **6** in only one step by an elegant carbocationic cascade cyclization. Precursor **6** can be prepared in enantiomerically pure form by a minor modification of the Knight synthesis via the chiral indolylacrylic acid imide **13**.

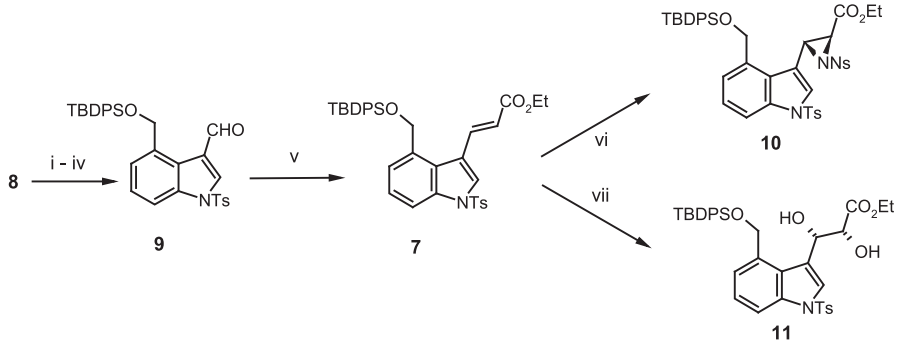


Scheme 1. Retrosynthetic analysis of CPA (**1**) according to the Knight synthesis.

2. Results and discussion

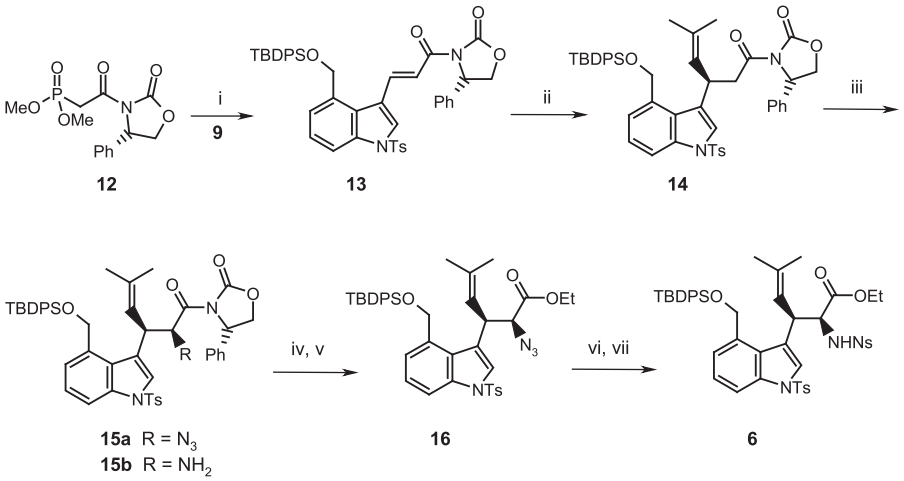
Indolyl-carbaldehyde **9** was prepared in four steps from commercially available indole-4-carboxylic acid methyl ester (**8**) (Scheme 2) according to literature procedures.[12–14] Our first approach towards intermediate **6** was based on a catalytic enantioselective aziridination of acrylic ester **7**. Enantioselective aziridinations of diverse cinnamic esters have been reported in several recent papers.[15–17] However, with PhINNs as electrophilic nitrogen source, catalytic amounts of $Cu(OTf)_2$ and the chiral ligand (+)-2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline], only very low yields of **10** were obtained, possibly due to the tosylate protected electron-poor indole system. On the other hand a catalytic enantioselective Sharpless dihydroxylation afforded diol **11** in sufficient yield but with low enantioselectivity (55% ee).[18,19]

By far better results were obtained with the classical Evans chiral oxazolidones, which controlled excellently both the 1,4-addition of isobutenyl cuprate and the 1,2-enolate addition of trisyl azide as electrophilic nitrogen source (Scheme 3). Due to their *syn*-arrangement only one auxiliary is needed to induce the correct absolute configuration at both chiral centers. Diastereomeric ratios of up to 94:6 were achieved in the Michael-addition and up to 98:2 in the azidation reaction with the (4*S*)-phenyloxazolidone auxiliary. Somewhat reduced selectivities were observed in the 1,4-addition with the (4*S*)-isopropyl- (85:15) and (4*S*)-benzyl-oxazolidones (83:17). In case of the one-carbon extended benzyl-oxazolidone the reduced induction can be explained by an unfavourable steric interaction with the bulky TBDPS-protecting group, which turns the benzyl group away from an ideal shielding position of the double bond. The indolylacrylic imide **13** was prepared in good yield by Horner–Emmons olefination of aldehyde **9** with the chiral phosphonic ester **12**.



Scheme 2. Synthesis of **7** and further transformations. Reagents: (i) $LiAlH_4$, THF, rt, 12 h, 94%; (ii) imidazole (3.0 equiv), TBDPSCl (1.7 equiv), DMF, 0 °C then rt, 12 h, 85%; (iii) DMF (3.5 equiv), $POCl_3$ (1.1 equiv), DMF, 0 °C then rt, 12 h, 78%; (iv) TsCl (1.5 equiv), NEt_3 (1.5 equiv), DCM, 12 h, 97%; (v) $(EtO)_2P(O)CH_2CO_2Et$ (2.4 equiv), LiCl (2.4 equiv), DBU (2.0 equiv), MeCN, 24 h, 83%; (vi) PhINNs (0.67 equiv), (+)-2,2′-isopropylidenebis[(4*R*)-4-phenyl-2-oxazoline] (0.067 equiv), $Cu(OTf)_2$ (0.033 equiv), DCM, rt, 12 h; (vii) methane sulfonamide (3 equiv), AD-mix alpha (0.01 equiv $K_2Os_2O_2(OH)_4$), ^{t}BuOH, H_2O, 24 h, rt.

Remarkably, reduction of the azide function in the oxazolidonyl imide **15a** and subsequent protection with the nosyl group proved to be significantly more difficult compared to ethyl ester **16**. While reduction of the azido group with $SnCl_2$ afforded 61% of the respective amine **15b**, nosylation of **15b** failed almost completely. The reduced reactivity of **15a** and **15b** (Scheme 3) can be attributed to a considerable sterical shielding of the azido group surrounded by the indolyl-/isobutenyl group on one side and the bulky oxazolidone on the other side. Consequently, the oxazolidone moiety was removed first using standard conditions (H_2O_2/LiOH) followed by esterification with K_2CO_3/EtI in 86% over two steps. As expected, the reduction (93%) and introduction of the nosyl group (87%) now



Scheme 3. Diastereoselective synthesis of key intermediate **6**. (i) **12** (1.2 equiv), KO^{t}Bu (1.0 equiv), THF, rt, 94% (ii) THF, thiophenol copper (1.0 equiv) then 2-methyl-1-propenylmagnesium bromide (3.0 equiv), −40 °C to rt, −60 °C to 0 °C, 1 h at 0 °C, 74%, dr 94:6 (iii) KHMDS 0.5 M in toluene, (1.1 equiv), −78 °C, add to **14** (1.0 equiv) in THF at −78 °C, then add enolate to trisyl azide (1.25 equiv), −78 °C, 3 min, hydrolyse with HOAc and warm up immediately to 30 °C, 30 min, 81%, dr 98:2; (iv) H_2O_2 30% (4 equiv), LiOH (2 equiv), THF/H_2O 3:1, 0 °C to rt, 2 h; (v) K_2CO_3 (5 equiv), EtI (3 equiv), acetone, rt, 18 h, 86% over two steps; (vi) $SnCl_2$ (2.0 equiv), MeOH, rt, 12 h, 89%; (vii) 4-$NO_2C_6H_4SO_2Cl$ (1.5 equiv), $^i Pr_2NEt$ (3.5 equiv), MeCN, 0 °C, 30 min, 87%.

succeeded in excellent yields to afford key intermediate **6**, from which CPA (**1**) is available in three additional steps according to the Knight synthesis.

3. Experimental section

3.1. General

Solvents and reagents were purchased from commercial sources. Triethylamine and diisopropylethylamine were dried over CaH_2 and distilled prior to use. Methanol was distilled from magnesium. Chloroform and dichloromethane were dried by passing the solvents through a basic aluminium oxide filled column. Precoated plates (silica gel 60 F_{254}, 250 μm, Merck, Darmstadt, Germany) were used for TLC. Silica gel 0.04–0.063 mm from Macherey–Nagel was used for chromatographic purification. HPLC-MS was performed on a Varian 500 IonTrap LC-ESI-MS system (column: 5 μm RP18). High-resolution MS were measured on a Bruker MicroTOF. Analytical ^{1}H and ^{13}C NMR spectra were recorded at 25 °C on a BRUKER AVANCE 400 (400.13 MHz for ^{1}H NMR, 100.62 MHz for ^{13}C NMR) or BRUKER AVANCE 600 (600.13 MHz for ^{1}H NMR, 150.90 MHz for ^{13}C NMR) spectrometer using tetramethylsilane as an internal standard. Melting points (mp) were determined with a Buechi 535 melting point apparatus and are uncorrected. IR-spectra were measured on a JASCO FT/IR-4200.

3.1.1. (S)-3-(2-Bromoacetyl)-4-phenyl-oxazolidin-2-one[20]. *n*-BuLi (1.6 M in hexane, 76.6 mL, 123 mmol) was added dropwise to a solution of (*S*)-4-phenyl-oxazolidin-2-one (20.0 g, 123 mmol) in dry THF (600 mL) at −78 °C under an inert gas atmosphere. The solution was warmed to −20 °C over a period of 30 min. After cooling again to −78 °C 2-bromoacetyl bromide (10.6 mL, 123 mmol) dissolved in dry THF (200 mL) was added and the mixture was allowed to warm up to room temperature. The reaction was hydrolysed with phosphate buffer (pH 7) and extracted with DCM. The combined organic layers were dried with Na_2SO_4 and the solvent was removed under reduced pressure. The crude product (33.0 g) was purified by column chromatography (cyclohexane/DCM 1/1) to yield (*S*)-3-(2-bromoacetyl)-4-phenyl-oxazolidin-2-one (25.3 g, 73%) as a colourless solid. The analytical and spectroscopic data are in accordance with those reported in the literature. R_f(cyclohexane/ethyl acetate 1/1): 0.41; mp 119.5–121.5 °C (lit[20]: 121–122 °C); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30–7.40 (m, 5H), 5.41 (dd, *J*=8.8, 3.9 Hz, 1H), 4.71 (t, *J*=8.8 Hz, 1H), 4.51 (d, *J*=12.3 Hz, 1H), 4.44 (d, *J*=12.6 Hz, 1H), 4.29 (dd, *J*=8.9, 3.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 165.3, 153.1, 138.0, 129.0 (CH), 128.8 (CH), 125.9 (CH), 70.3 (CH_2), 57.7 (CH), 27.9 (CH_2); ESI-MS *m*/*z* (%)= 284.0 (96, $[M+H]^+$), 286.0 (100, $[M+H]^+$), 301.0 (26, $[M+NH_4]^+$), 303.0 (26, $[M+NH_4]^+$), 589.0 (4, $[2M+Na]^+$), 591.0 (4, $[2M+Na]^+$).

*3.1.2. (S)-Dimethyl 2-oxo-2-(2-oxo-4-phenyl-oxazolidin-3-yl) ethylphosphonate (**12**).* Freshly distilled trimethyl phosphite (55 mL, 465 mmol) was added to (*S*)-3-(2-bromoacetyl)-4-phenyl-oxazolidin-2-one (41.4 g, 146 mmol). The reaction mixture was stirred for 3 h at 55–60 °C. Then the excess trimethyl phosphite was removed in vacuo. Crystallization of the crude product from ethyl acetate yielded **12** (44.1 g, 97%) as a colourless solid. R_f (ethyl acetate): 0.24; mp 110.3–112.7 °C; $[\alpha]_D^{25}$ +78.8 (*c* 1.0, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29–7.38 (m, 5H), 5.44 (dd, *J*=8.7, 3.9 Hz, 1H), 4.68 (t, *J*=8.9 Hz, 1H), 4.26 (dd, *J*=9.0, 3.9 Hz, 1H), 3.73 (d, *J*=3.5 Hz, 3H), 3.71 (d, *J*=3.5 Hz, 3H), 3.69–3.86 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2 (d, *J*=6.8 Hz), 153.5, 138.4, 129.0 (CH), 128.7 (CH), 126.0 (CH), 69.8 (CH_2), 57.8 (CH), 53.0, 53.1 (2×d, CH_3), 34.3 (d, *J*=130.4 Hz, CH_2); ^{31}P NMR (162 MHz, $CDCl_3$): δ 23.08; HR-ESI-MS *m*/*z*=336.0606 (calcd 336.0607 for $C_{13}H_{16}NO_6PNa$); IR: *v* 1771, 1676, 1607 cm^{-1}.

*3.1.3. (S)-3-{(E)-3-[4-(tert-Butyl-diphenyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-acryloyl}-4-phenyl-oxazolidin-2-one (**13**).* KO^{t}Bu (4.0 g, 35.2 mmol) was added to a solution of **12** (13.2 g, 42.3 mmol) in THF (375 mL). The solution was stirred for 30 min at room temperature followed by dropwise addition of indolylaldehyde **9** (20.0 g, 35.2 mmol) in THF (375 mL). The reaction was stirred over night, neutralized with aqueous saturated ammonium chloride solution and extracted three times with DCM. The combined organic layers were dried over Na_2SO_4. After removal of the solvent and chromatographic purification (cyclohexane/ethyl acetate 10/1 and cyclohexane/ethyl acetate 4/1) starting material (6.25 g) and pure **13** (17.2 g, 65%, foam) were obtained. R_f (DCM): 0.35; $[\alpha]_D^{25}$ +22.0 (*c* 1.02, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.27 (d, *J*=15.4 Hz, 1H), 8.05 (s, 1H), 7.91 (d, *J*=8.3 Hz, 1H), 7.82 (d, *J*=8.3 Hz, 2H), 7.79 (d, *J*=15.4 Hz, 1H), 7.64 (m, 4H), 7.17–7.40 (m, 14H), 7.02 (d, *J*=7.4 Hz, 1H), 5.56 (dd, *J*=8.7, 3.9 Hz, 1H), 4.95 (s, 2H), 4.74 (t, *J*=8.7 Hz, 1H), 4.33 (dd, *J*=8.8, 3.7 Hz, 1H), 2.36 (s, 3H), 0.93 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 153.9, 145.4, 139.3, 139.2 (CH), 135.7 (CH), 135.7 (CH), 135.6 (C), 134.9, 134.1, 133.3, 133.2, 130.0 (CH), 129.6 (CH), 129.5 (CH), 129.1 (CH), 128.6 (CH), 127.5 (CH), 127.5 (CH), 127.2, 127.1 (CH), 126.9, 126.1 (CH), 125.4 (CH), 124.8 (CH), 123.5 (CH), 119.5, 117.4 (CH), 113.1 (CH), 70.0 (CH_2), 64.5

(CH_2), 57.8 (CH), 26.7 (CH_3), 21.6 (CH_3), 19.1; HR-ESI-MS m/z=777.2427 (calcd 777.2425 for $C_{44}H_{42}N_2O_6SSiNa$); IR: ν 1770, 1682 cm^{-1}.

*3.1.4. (S)-3-{(R)-3-[4-(tert-Butyl-diphenyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-5-methyl-hex-4-enoyl}-4-phenyl-oxazolidin-2-one (**14**).* Thiophenol copper (1.72 g, 9.93 mmol) was suspended in THF (37.5 mL) under inert gas atmosphere and cooled to −40 °C. (2-Methylprop-1-enyl)magnesium bromide (59.6 mL, 29.8 mmol) was added dropwise over a period of 10 min. The solution was warmed to room temperature and stirred for 20 min. After cooling to −60 °C indolylacrylic imide **13** (7.50 g, 9.93 mmol) in THF (12.5 mL) was added dropwise over a period of 20 min. After stirring for 1 h at 0 °C the solution was poured into cold saturated aqueous ammonia (200 mL), stirred for 15 min at room temperature and extracted three times with DCM (100 mL). Drying and removal of the solvent under reduced pressure afforded a crude product (7.85 g), which was purified by column chromatography (DCM) to yield the Michael-addition product **14** (5.96 g, 74%) as a yellowish foam. R_f (DCM): 0.59; $[\alpha]_D^{25}$ +17.0 (c 1.0, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.88 (d, J=8.2 Hz, 1H), 7.72 (d, J=8.3 Hz, 2H), 7.63–7.66 (m, 4H), 7.48 (d, J=7.3 Hz, 1H), 7.39 (s, 1H), 7.10–7.37 (m, 14H), 5.26 (d, J=15.0 Hz, 1H), 5.23 (dd, J=9.0, 4.1 Hz, 1H), 5.09 (d, J=14.0 Hz, 1H), 5.00 (d, J=9.0 Hz, 1H), 4.57 (t, J=8.8 Hz, 1H), 4.26 (q, J=7.6 Hz, 1H), 4.17 (dd, J=8.8, 3.9 Hz, 1H), 3.29 (dd, J=16.2, 7.5 Hz, 1H), 3.16 (dd, J=16.2, 7.5 Hz, 1H), 2.34 (s, 3H), 1.42 (s, 3H), 1.08 (s, 3H), 1.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.0, 153.6, 144.6, 138.8, 135.6 (CH), 135.4, 135.3, 134.7, 133.5, 133.4, 133.4, 129.7 (CH), 129.5 (CH), 129.5 (CH), 128.9 (CH), 128.4 (CH), 127.6 (CH), 127.2, 127.0 (CH), 126.8 (CH), 126.6, 126.3, 125.7 (CH), 124.4 (CH), 123.0 (CH), 120.8 (CH), 112.3 (CH), 69.8 (CH_2), 63.2 (CH_2), 57.4 (CH), 41.8 (CH_2), 32.7 (CH), 26.8 (CH_3), 25.4 (CH_3), 21.5 (CH_3), 19.3, 17.7 (CH_3); HR-ESI-MS m/z=833.3056 (calcd 833.3051 for $C_{48}H_{50}N_2O_6SSiNa$); IR: ν 1778, 1703 cm^{-1}.

*3.1.5. (S)-3-{(2S,3R)-2-Azido-3-[4-(tert-Butyl-diphenyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-5-methyl-hex-4-enoyl}-4-phenyl-oxazolidin-2-one (**15a**).* A solution of **14** (23.2 g, 28.5 mmol) in THF (65 mL) was cooled to −78 °C and transferred through a metal cannula to a KHMDS (62.8 mL, 0.5 M in toluene, 31.4 mmol) solution in THF (65 mL) at −78 °C. Stirring was continued for 90 min at this temperature and the resulting solution transferred through a metal cannula into a stirred solution of trisyl azide (11.0 g, 35.7 mmol) in THF (65 mL) at −78 °C. After 3 min the reaction was stopped by addition of acetic acid (8.2 mL, 142.7 mmol), immediately warmed to 30 °C and stirred for 30 min at this temperature. Water was added (500 mL) and the solution was extracted three times with DCM (250 mL). After drying and removal of the solvent a crude product (33.0 g) was obtained, which was purified by column chromatography (DCM/CH 7:3) to afford **15a** (17.6 g, 73%) as a colourless foam. R_f (DCM): 0.5; $[\alpha]_D^{25}$ +12.9 (c 1.0, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.87 (d, J=8.4 Hz, 1H), 7.79 (d, J=8.3 Hz, 2H), 7.60–7.66 (m, 5H), 7.49 (s, 1H), 7.14–7.37 (m, 14H), 5.46 (d, J=14.1 Hz, 1H), 5.35 (d, J=10.0 Hz, 1H), 5.08 (d, J=10.4 Hz, 1H), 5.05 (d, J=14.2 Hz, 1H), 4.85 (dd, J=8.5, 3.6 Hz, 1H), 4.21 (t, J=8.8 Hz, 1H), 4.19 (t, J=9.9 Hz, 1H), 4.09 (dd, J=8.9, 3.6 Hz, 1H), 2.37 (s, 3H), 1.54 (s, 3H), 1.17 (s, 3H), 1.08 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 153.0, 145.0, 138.1 (CH), 136.7, 135.5 (CH), 135.5 (CH), 135.4, 135.3, 134.7, 133.5, 133.2, 129.9 (CH), 129.6 (CH), 129.2 (CH), 128.8 (CH), 127.7 (CH), 127.7 (CH), 127.1 (CH), 125.8, 125.7 (CH), 124.8 (CH), 123.9 (CH), 123.6 (CH), 122.6, 120.4 (CH), 111.9 (CH), 70.0 (CH_2), 63.8 (CH), 63.1 (CH_2), 57.6 (CH), 38.5 (CH), 26.9 (CH_3), 25.7 (CH_3), 21.6 (CH_3), 19.4, 18.2 (CH_3); HR-ESI-MS m/z=874.3063 (calcd 874.3065 for $C_{48}H_{49}N_5O_6SSiNa$); IR: ν 1777, 1702 cm^{-1}.

*3.1.6. (2S,3S)-3-[4-(tert-Butyl-diphenyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-2,5-dimethyl-hex-4-enoic acid ethyl ester (**16**).* Compound **15a** (37.0 g, 31.7 mmol) was dissolved in THF (160 mL), water (50 mL) was added and the resulting solution was cooled to 0 °C. Then H_2O_2 (12.9 mL, 30%, 126.7 mmol) and LiOH (1.5 g, 63.3 mmol) were added. The reaction mixture was warmed to room temperature and stirred for 2 h. After recooling to 0 °C aqueous Na_2SO_3 solution (80 mL, 1.5 M, 139 mmol) was added followed by saturated aqueous ammonium chloride (160 mL) solution. The mixture was extracted three times with DCM (100 mL) and the combined organic layers were dried with Na_2SO_4. After removal of the solvent the residue was dried under high vacuum and used for the subsequent reaction without further purification. K_2CO_3 (21.9 g, 158.3 mmol) and EtI (7.6 mL, 95.0 mmol) were added to a solution of the crude acid (26.8 g) in acetone (50 mL). The reaction mixture was stirred for 2 h at room temperature. After that time the solvent was removed, the residue resolved in DCM and washed with a saturated aqueous ammonium chloride solution. The crude product (27.2 g) obtained after drying and removal of the solvent was purified by column chromatography (DCM/cyclohexane 7/3) to yield ethyl ester **16** (20.0 g, 86%) as a yellow foam. R_f(cyclohexane/ethyl acetate 1/1): 0.60; $[\alpha]_D^{25}$ +5.9 (c 1.0, DCM); ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.94 (d, J=8.2 Hz, 1H), 7.77 (d, J=8.3 Hz, 2H), 7.63–7.69 (m, 4H), 7.52 (s, 1H), 7.23–7.45 (m, 10H), 5.38 (d, J=9.4 Hz, 1H), 5.19–5.27 (m, 2H), 4.40 (dd, J=9.4, 4.3 Hz, 1H), 3.95–4.03 (m, 2H), 3.82–3.90 (m, 1H), 2.37 (s, 3H), 1.69 (s, 3H), 1.38 (s, 3H), 1.01 (s, 9H), 0.97 (t, J=7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 168.5, 144.9, 136.2, 135.6 (CH), 135.5 (CH), 135.2, 135.1, 134.0, 133.3, 133.1, 129.8 (CH), 129.8 (CH), 127.7 (CH), 127.7 (CH), 126.9 (CH), 126.1, 125.6 (CH), 124.5 (CH), 122.6, 121.9 (CH), 120.7 (CH), 112.8 (CH), 66.3 (CH), 63.6 (CH_2), 61.6 (CH_2), 38.5 (CH), 26.8 (CH_3), 25.7 (CH_3), 21.5 (CH_3), 19.3, 18.5 (CH_3), 13.8 (CH_3); HR-ESI-MS m/z=757.2848 (calcd 757.2850 for $C_{41}H_{46}N_4O_5SSiNa$); IR: ν 1731, 1598 cm^{-1}.

*3.1.7. (2S,3R)-3-[4-(tert-Butyl-diphenyl-silanyloxymethyl)-1-(toluene-4-sulfonyl)-1H-indol-3-yl]-5-methyl-2-(4-nitro-benzenesulfonyl-amino)-hex-4-enoic acid ethyl ester (**6**).* Compound **16** (7.78 g, 10.6 mmol) was dissolved in MeOH (100 mL), $SnCl_2$ (4.78 g, 21.2 mmol) was added and the resulting mixture was stirred over night at room temperature. The solvent was removed under reduced pressure, water (50 mL) and aqueous sodium hydroxide (6 M, 0.5 mL) were added to the residue and the mixture was stirred for 20 min at room temperature. Threefold extraction with DCM, followed by removal of the solvent afforded the crude amine (6.67 g, 89%) as a yellowish foam. R_f(cyclohexane/ethyl acetate 1/1): 0.40; ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.93 (s, 1H), 7.87–7.90 (m, 3H), 7.62–7.68 (m, 4H), 7.38–7.42 (m, 2H), 7.29–7.34 (m, 5H), 7.21–7.23 (m, 3H), 5.72 (d, J=9.5 Hz, 1H), 5.15–5.22 (m, 2H), 4.52 (d, J=9.5, 4.0 Hz, 1H), 4.02 (br d, 1H), 3.93 (q, J=7.1 Hz, 2H), 2.33 (s, 3H), 1.65 (s, 3H), 1.31 (s, 3H), 1.07 (s, 9H), 0.91 (t, J=7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 168.8, 144.7, 137.9, 135.5 (CH), 135.5 (CH), 135.2, 135.0, 133.9, 133.3, 133.1, 129.8 (CH), 129.7 (CH), 129.7 (CH), 127.7 (CH), 127.2 (CH), 126.1, 125.8 (CH), 124.4 (CH), 121.6 (CH), 119.8 (CH), 112.6 (CH), 63.6 (CH_2), 62.2 (CH_2), 58.2 (CH), 57.5 (CH), 37.7 (CH), 26.8 (CH_3), 25.7 (CH_3), 21.5 (CH_3), 19.3, 18.6 (CH_3), 13.6 (CH_3); HR-ESI-MS m/z=709.3124 (calcd 709.3126 for $C_{41}H_{49}N_2O_5SiNa$); IR: ν=3386, 1731 cm^{-1}.

The crude material of the previous reaction (6.67 g, 9.40 mmol) was dissolved in dry MeCN (80 mL) and 4-nitrobenzene-1-sulfonyl chloride (3.13 g, 14.10 mmol) was added at 0 °C followed by ^{i}Pr$_2$NEt (5.6 mL, 32.91 mmol). After a reaction time of 30 min at 0 °C the solvent was removed under reduced pressure. The residue was partitioned between a saturated aqueous ammonium chloride solution and DCM. The aqueous phase was extracted twice with DCM. The crude product (9.29 g) obtained after drying and removal of the solvent was purified by column chromatography (cyclohexane/ethyl acetate 1/1) to yield the nosyl protected key intermediate **6** (7.27 g, 87%) as a yellow foam. R_f (cyclohexane/ethyl acetate 1/1): 0.70; $[\alpha]_D^{25}$ −15.1 (c 1.0, DCM); ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.92–7.94 (m, 2H), 7.75 (d, J=8.5 Hz, 2H), 7.68–7.70 (m, 3H),

7.62–7.63 (m, 2H), 7.48–7.50 (m, 2H), 7.41–7.45 (m, 2H), 7.41 (s, 1H), 7.36 (t, J=7.4 Hz, 2H), 7.33 (t, J=7.6 Hz, 2H), 7.24 (d, J=8.3 Hz, 2H), 7.21 (d, J=7.3 Hz, 1H), 7.16 (t, J=7.8 Hz, 1H), 5.61 (br d, J=9.6 Hz, 1H), 5.34 (d, J=13.2 Hz, 1H), 5.10 (d, J=13.5 Hz, 1H), 4.03 (br dd, J=9.7, 3.2 Hz, 1H), 3.88–3.97 (m, 2H), 2.34 (s, 3H), 1.72 (s, 3H), 1.36 (s, 3H), 1.09 (s, 9H), 0.99 (t, J=7.1 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$): δ=169.8, 149.6, 145.0, 144.6, 137.4, 135.5 (CH), 135.5 (CH), 134.9, 134.8, 133.5, 133.2, 133.1, 129.8 (CH), 129.8 (CH), 127.7 (CH), 127.6 (CH), 127.5 (CH), 126.9 (CH), 125.6, 125.3 (CH), 124.4 (CH), 123.8 (CH), 122.0 (CH), 121.1, 118.4 (CH), 112.5 (CH), 63.6 (CH_2), 62.0 (CH_2), 59.9 (CH), 38.1 (CH), 26.8 (CH_3), 25.8 (CH_3), 21.5 (CH_3), 19.2, 18.5 (CH_3), 13.8 (CH_3); HR-ESI-MS m/z=892.2769 (calcd 892.2763 for $C_{47}H_{50}N_3O_9S_2Si$); IR: ν 3284, 1736 cm^{-1}.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.06.092.

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