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Scalable synthesis of the unusual amino acid segment (ADMOA unit) of marine anti-inflammatory peptide: solomonamide A†

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The most abundantly available hexose sugar, D-glucose has been converted to protected 4-amino-(2′amino-4′-hydroxy phenyl)-3,5-dihydroxy-2-methyl-6-oxo hexanoic acid (protected ADMOA, **3**), the unusual amino acid present in marine natural product solomonamide A in gram quantities involving easy to operate chemical transformations.

Introduction

The cyclic peptide natural products originating from marine sources have tremendous potential as drug leads.[1] Also, some of these natural peptides incorporate non-proteinogenic (uncommon) amino acids which add new properties to these natural products.[2] These uncommon amino acids provide additional stability to enzyme degradation and provide three dimensional shapes for better biological activities.[3] A good number of marine peptides have been taken into chemical development *viz.* dolastatin,[4] didemnins,[5] auristatin,[6] ecteinascidin 743.[7]

Zampella's group has isolated two cyclic peptides, namely solomonamides A and B (Fig. 1, **1** and **1a**),[8] from the marine sponge *Theonella swinhoei* and have characterized and assigned structures based on extensive spectral studies. Solomonamide A has one unusual amino acid, 4-amino(2′-amino-4′-hydroxy phenyl)-3,5-dihydroxy-2-methyl-6-oxo hexanoic acid (ADMOA, **2**) and solomonamide B has a similar amino acid except that it lacks one hydroxy group at the 5′-position and is named as AHMOA, **2a**. Solomonamide A was the minor component of several molecules isolated from *Theonella* species and the biological targets are not validated owing to scarcity of the natural product, except that some *in vivo* studies indicated anti-inflammatory properties (100 μg per kg weight). Thus, the synthesis of the natural product and its analogues would be of utmost desire to explore further potential of this natural product. Besides, the very uncommon γ-amino acid (ADMOA, **2**) poses a synthetic challenge owing to the presence of multiple and adjacent chiral centers.

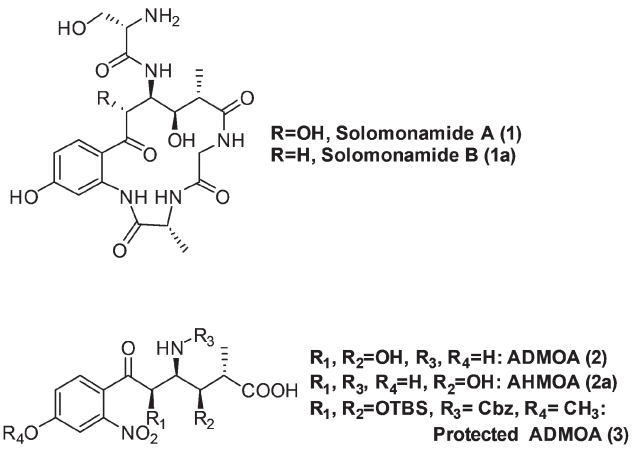

Fig. 1 Structure of solomonamide A, B and their unusual amino acid units.

The synthetic efforts from our own research group[9] and the group of Reddy[10] are far from accomplishing the total synthesis. It is thought that the accomplishment of a scalable synthesis of the most functionalized part of solomonamide A, namely protected ADMOA **3**, will pave the way for the total synthesis of solomonamide and related peptides along with simplified analogues rather efficiently.

Results and discussion

In this regard, a general and scalable synthetic route involving readily accessible chemicals is conceived. D-Glucose, undoubtedly the cheapest chiral precursor,[11] which already has most of the necessary chiral centers built in, was chosen as the starting

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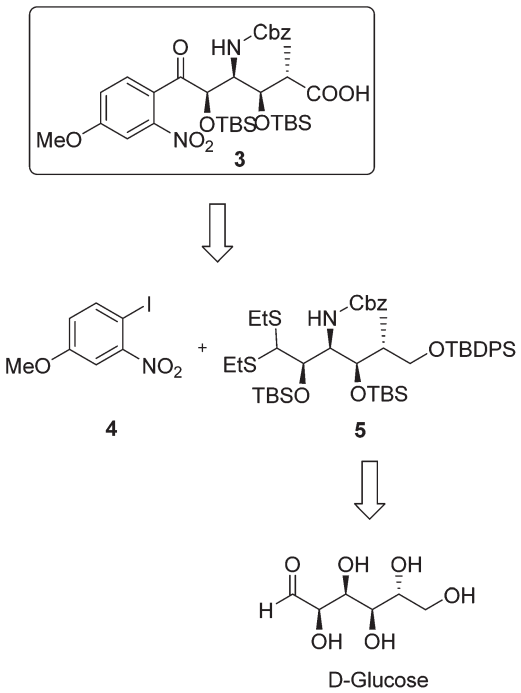
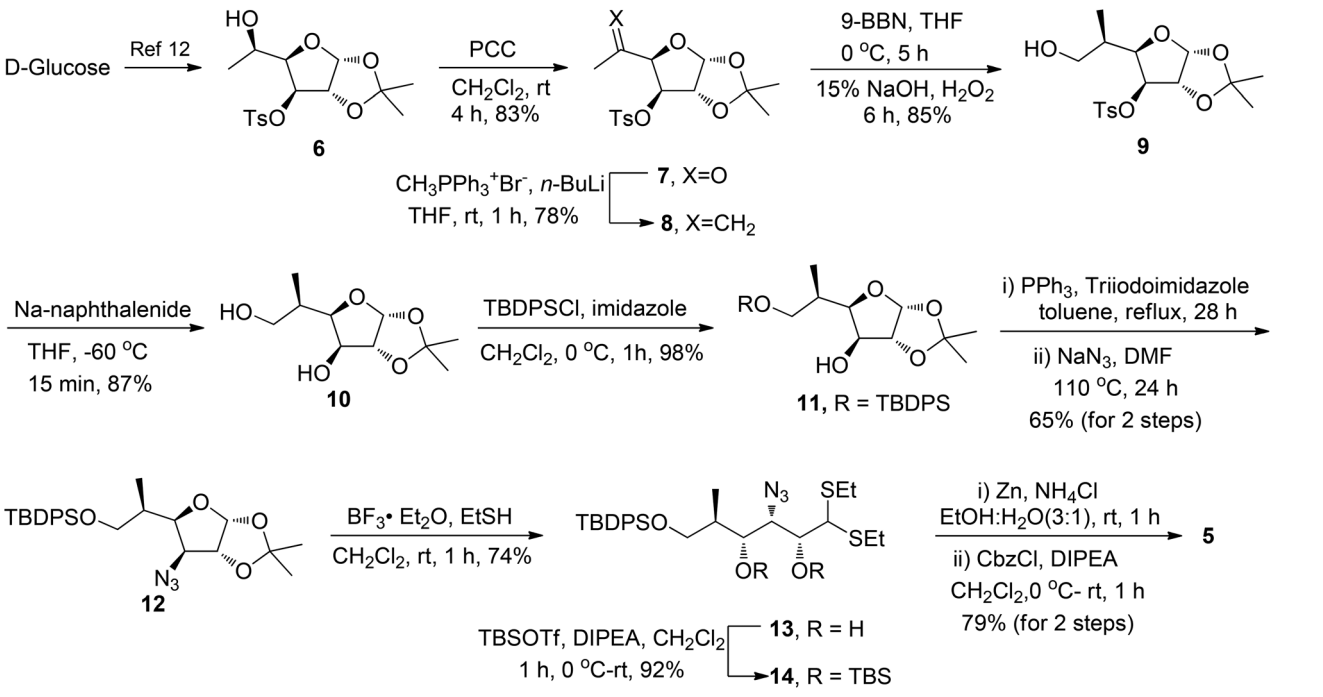


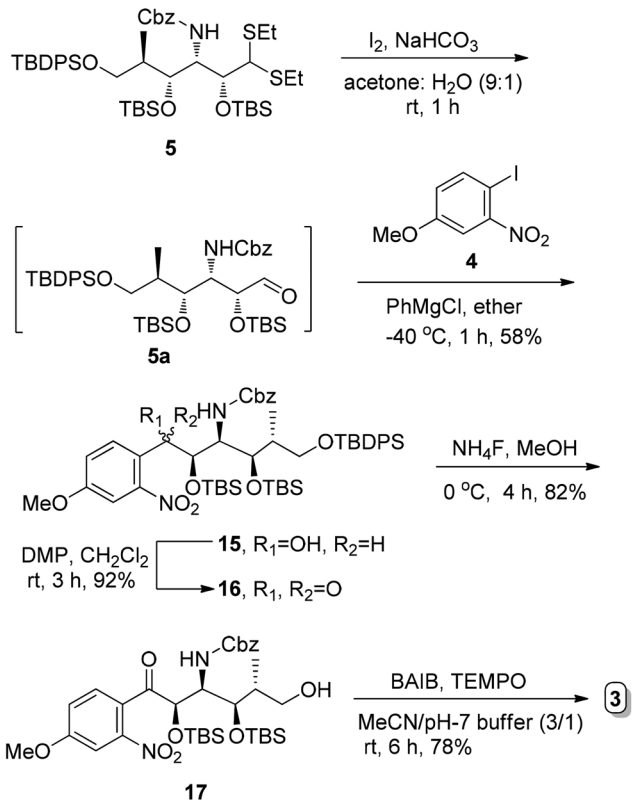
Scheme 1 Retrosynthetic analysis of protected ADMOA **3**.

material to make intermediate **5**, based on the retrosynthesis shown in Scheme 1. Grignard reaction on the unmasked thioacetal **5** with nitro aryl iodide **4** would provide the aromatic part to realize the uncommon and protected ADMOA fragment **3**.

The desired furanose derivative **6** was prepared from D-glucose following a literature procedure.[12,13] Pyridinium chlorochromate (PCC) mediated oxidation of alcohol **6** to methyl ketone **7** was achieved in 83% yield. One carbon homologation using methylenetriphenylphosphorane (*in situ* generated from methyltriphenylphosphonium bromide and *n*-BuLi) provided 5-deoxy sugar **8** in 78% yield.[14] Substrate controlled diastereoselective hydroboration of the olefin in the presence of 9-BBN furnished furano alcohol **9**, with 20 : 1 de in favour of the required isomer, and the major isomer was separated by silica gel column chromatography in pure form (85% yield).[12] Similar hydroboration on 3′-*O*-benzyl protected substrate provided low diastereoselectivity, which compelled us to switch to tosyl protection at the 3′-position. The tosyl group at the 3′ position in **9** was removed using Na-naphthalenide[15] to give the diol **10** (87%), and the selective protection of the primary alcohol as TBDPS ether gave **11** in 98% yield. The double inversion technique was employed to install the azido group at the 3′ position wherein the treatment of **11** with triphenylphosphine, triiodoimidazole[16] furnished iodo with *allo*-configuration which upon treatment with NaN_3 furnished azido furanose with *xylo*-configuration to provide **12** in 65% yield over two steps. Classical ring opening of 1,2-*O*-isopropylidene furan in **12** with EtSH and $BF_3{\cdot}OEt_2$ as catalyst provided the acyclic dithiane **13** in 74% yield.[17] For operational simplicity the diol functionality was silylated to provide trisilyl derivative **14** in 92% yield. Metal catalyzed reduction (Zn/NH_4Cl) of azide to amine followed by treatment with Cbz–Cl gave the carbamate **5** in 79% yield (Scheme 2).



Scheme 2 Synthesis of compound **5**.



Scheme 3 Synthesis of compound **3**.

The masked aldehyde functionality in **5** was released to free aldehyde **5a** using iodine in the presence of sodium bicarbonate,[18] which underwent Grignard reaction with nitro aryl iodide **4** in the presence of PhMgCl (metal–halogen exchange) to furnish the diastereomeric alcohol **15** in 58% yield.[19] Oxidation of **15** using Dess–Martin periodinane (DMP) gave enantiopure keto derivative **16** in 92% yield. Selective deprotection of the TBDPS group at the primary end with NH_4F in methanol gave the alcohol **17** which upon one-pot oxidation using (diacetoxyiodo)benzene (BAIB)/2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)[20] provided free carboxylic acid **3** in 78% yield (Scheme 3).[21,22] The acid **3** has built in all the required chiral centers of ADMOA and also is differentially protected for utility of this in a total synthesis.

Experimental

General information

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using 300, 400 or 500 MHz spectrometers at ambient temperature. Chemical shifts were measured in ppm and coupling constants in hertz (Hz). The shifts were measured relative to the signals for residual $CHCl_3$ (7.26 ppm), $CDCl_3$ (77.0 ppm). All ^{13}C NMR spectra were proton decoupled. Optical rotations were measured on a digital polarimeter operating on the sodium D line with a 1 mL cell with a 1 dm path length. Infrared (IR) spectra were obtained using either thin films (for oils) or a KBr matrix (for solids). Commercially available reagents were used, unless otherwise indicated. Tetrahydrofuran was distilled under nitrogen from Na-benzophenone prior to use. CH_2Cl_2 was dried over 4 Å molecular sieves. Technical grade ethyl acetate and hexanes used for column chromatography were distilled prior to use. Column chromatography was carried out with silica gel (60–120 mesh) packed in glass columns. All the reactions were performed under nitrogen in oven-dried glassware with magnetic stirring.

(3a*R*,5*S*,6*R*,6a*R*)-5-Acetyl-2,2-dimethyltetrahydrofuro[2,3-*d*]-[1,3]dioxol-6-yl 4-methylbenzenesulfonate (7). To a suspension of pyridinium chlorochromate (PCC, 9.0 g, 41.8 mmol) and finely powdered 4 Å molecular sieves (2.0 g) in anhydrous CH_2Cl_2 (80 mL) was added a solution of **6** (7.5 g, 20.9 mmol) in anhydrous CH_2Cl_2 (25 mL). The mixture was stirred at room temperature for 4 h. After consumption of starting material (by TLC profile), the mixture was diluted with ether (100 mL). The precipitates were filtered off through Celite, washed with ether (50 mL) and the ether layer was evaporated *in vacuo*. The residue was purified by column chromatography with EtOAc–pet. ether (1 : 5) as an eluant to give **7** (6.1 g, 83%) as a colorless syrup.

$[\alpha]_D^{25} = -88.51$ (c = 2.39, $CHCl_3$); {lit. $[\alpha]_D^{20} = -47.88$ (c = 1.4, MeOH)};[12] IR (neat): ν_{max} 2989, 1726, 1371, 1217, 1028, 849, 717 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.70 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 6.07 (d, J = 3.5 Hz, 1H), 4.94 (d, J = 3.2 Hz, 1H), 4.83 (d, J = 3.5 Hz, 1H), 4.56 (d, J = 3.3 Hz, 1H), 2.45 (s, 3H), 2.13 (s, 3H), 1.44 (s, 3H), 1.30 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 203.9, 145.6, 131.8, 129.9, 128.0, 112.8, 105.3, 83.4, 82.6, 27.8, 26.5, 26.1, 21.6; HRMS (ESI): m/z calculated for $C_{16}H_{20}NaO_7S$: $[M + Na]^+$ 379.0822, found 379.0860.

(3a*R*,5*R*,6*S*,6a*R*)-2,2-Dimethyl-5-(prop-1-en-2-yl)tetrahydrofuro-[2,3-*d*][1,3]dioxol-6-yl4-methylbenzenesulfonate (8). A stirred solution of methylenetriphenylphosphorane {prepared from *n*-BuLi (13.4 mL, 2.5 M in hexane, 33.7 mmol) and methyltriphenylphosphonium bromide (15.0 g, 42.1 mmol) in THF (50 mL)} was added dropwise to a solution of the ketone **7** (6.0 g, 16.8 mmol) in THF (30 mL) at room temperature. After 1 h, the reaction mixture was poured into ice-water (50 mL) and extracted with EtOAc (2 × 75 mL). The extracts were washed with water, dried, and evaporated under reduced pressure, and the crude residue was chromatographed on a silica gel column with pet. ether–EtOAc (10 : 1) as eluant to afford the product **8** as oil (4.6 g, 78%).

$[\alpha]_D^{25} = -13.36$ (c = 1.09, $CHCl_3$); IR (neat): ν_{max} 2930, 2857, 1675, 1043, 699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.74 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.1 Hz, 2H), 5.91 (d, J = 3.6 Hz, 1H), 5.03 (s, 1H), 4.87 (d, J = 1.1 Hz, 1H), 4.75 (d, J = 2.6 Hz, 1H), 4.65 (d, J = 3.7 Hz, 1H), 4.53 (s, 1H), 2.46 (s, 3H), 1.51 (s, 3H), 1.47 (s, 3H), 1.29 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 145.2, 136.6, 132.8, 129.8, 127.9, 113.5, 112.2, 104.2, 83.1, 81.9, 80.9, 26.5, 26.1, 21.6, 19.2; HRMS (ESI): m/z calculated for $C_{17}H_{23}O_6S$: $[M + H]^+$ 355.1209, found 355.1227.

(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-1-Hydroxypropan-2-yl)-2,2-dimethyl-tetrahydrofuro[2,3-*d*][1,3]dioxol-6-yl4-methyl benzenesulfonate

(9). To a stirred solution of olefin **8** (4.5 g, 12.7 mmol) in THF (30 mL) was added a 1 M solution of 9-BBN in THF (13.9 mL, 13.9 mmol) at 0 °C. After 5 h, aqueous 15% NaOH (112.5 mL) and 30% H_2O_2 (67.5 mL) were added slowly, and the mixture was stirred vigorously for 6 h. The aqueous layer was extracted with EtOAc (3 × 50 mL). The organic extracts were washed with water, dried (Na_2SO_4), evaporated under reduced pressure, and purified by silica gel chromatography with pet. ether–EtOAc (1 : 2) as eluant to afford **9** (4.0 g, 85%).

$[\alpha]_D^{25}$ = −31.18 (*c* = 3.17, $CHCl_3$); {lit. $[\alpha]_D^{20}$ = −35.0 (*c* = 1.27, $CHCl_3$)};[12] IR (neat): ν_{max} 3429, 2979, 2936, 1372, 1216, 1019 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.82 (d, *J* = 8.3 Hz, 2H), 7.38 (d, *J* = 8.1 Hz, 2H), 5.89 (d, *J* = 3.7 Hz, 1H), 4.84 (d, *J* = 2.4 Hz, 1H), 4.68 (d, *J* = 3.7 Hz, 1H), 4.03–3.96 (dd, *J* = 2.4, 10.1 Hz, 1H), 3.60 (d, *J* = 5.0 Hz, 2 H), 2.46 (s, 3H), 2.04–1.91 (m, 1H), 1.48 (s, 3H), 1.28 (s, 3H), 0.62 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 145.4, 132.8, 129.9, 127.7, 112.1, 104.2, 82.4, 81.8, 66.0, 33.6, 26.3, 26.0, 21.6, 12.3; HRMS (ESI): *m*/*z* calculated for $C_{17}H_{24}NaO_7S$: $[M + Na]^+$ 395.1135, found 395.1167.

(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-1-Hydroxypropan-2-yl)-2,2-dimethyltetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (10). Finely chopped sodium metal (2.3 g, 103.0 mmol) and naphthalene (4.4 g, 34.3 mmol) were dissolved in anhydrous THF (100 mL) and the mixture was subjected to ultrasonic irradiation for 30 min to provide a dark green solution (stock solution, stored at −20 °C). The desired *O*-tosyl compound **9** (4.0 g, 10.7 mmol) in THF (40 mL) was cooled to −60 °C and the Na-naphthalenide solution was added dropwise to the reaction *via* syringe, until a dark green color persisted for 5 min. The reaction was quenched with aqueous NH_4Cl (to discharge the green color) and the reaction was diluted with ether (50 mL). The ether layer was separated and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated. Purification by silica gel chromatography using hexanes–EtOAc (1 : 1) as eluant provided the diol product **10** (2.0 g, 87% yield).

$[\alpha]_D^{25}$ = −26.87 (*c* = 2.94, $CHCl_3$); IR (neat): ν_{max} 3384, 2936, 2880, 1214, 1071, 1009, 782, 654 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.85 (d, *J* = 3.7 Hz, 1H), 4.44 (d, *J* = 3.7 Hz, 1H), 4.03 (d, *J* = 2.2 Hz, 1H), 3.89–3.83 (dd, *J* = 2.2, 9.0 Hz, 1H), 3.72–3.64 (dd, *J* = 6.7, 10.5 Hz, 1H), 3.63–3.50 (m, 3H), 2.16–2.02 (m, 1H), 1.46 (s, 3H), 1.28 (s, 3H), 0.92 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 111.4, 104.3, 84.6, 84.2, 74.5, 66.1, 33.9, 26.4, 25.9, 13.3; HRMS (ESI): *m*/*z* calculated for $C_{10}H_{18}NaO_5$: $[M + Na]^+$ 241.1046, found 241.1064.

(3a*R*,5*R*,6*S*,6a*R*)-5-((*R*)-1-(*tert*-Butyldiphenylsilyloxy)propan-2-yl)-2,2-dimethyl tetrahydrofuro[2,3-*d*][1,3]dioxol-6-ol (11). To a stirred solution of compound **10** (2.0 g, 9.1 mmol) in anhydrous CH_2Cl_2 (20 mL) at 0 °C under nitrogen atmosphere was added imidazole (1.5 g, 22.9 mmol). After stirring for 5 min, TBDPS-Cl (2.7 g, 10.0 mmol) and DMAP (0.1 g, 0.9 mmol) were added to the reaction mixture. After 1 h, the reaction mixture was quenched with aqueous NH_4Cl (10 mL) and the product was extracted with $CHCl_3$ (2 × 20 mL). The combined organic layers were washed with brine (50 mL), dried (Na_2SO_4), and concentrated under vacuum. Purification by silica gel column chromatography using hexanes–EtOAc (4 : 1) afforded compound **11** (4.0 g, 98%) as colorless oil.

$[\alpha]_D^{25}$ = −21.42 (*c* = 1.12, $CHCl_3$); IR (neat): ν_{max} 3429, 2933, 2860, 1379, 1215, 1074, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.75–7.65 (m, 4H), 7.47–7.34 (m, 6H), 5.92 (d, *J* = 3.7 Hz, 1H), 4.53 (d, *J* = 3.8 Hz, 1H), 4.20–4.11 (m, 2H), 3.81–3.74 (dd, *J* = 4.5, 9.9 Hz, 1H), 3.73–3.67 (dd, *J* = 4.5, 9.9 Hz, 1H), 2.65 (d, *J* = 5.8 Hz, 1H), 2.09–1.97 (m, 1H), 1.47 (s, 3H), 1.32 (s, 3H), 1.07 (d, *J* = 7.5 Hz, 3H), 1.05 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.6, 135.5, 133.3, 133.1, 129.5, 127.6, 111.3, 104.3, 85.1, 81.3, 75.1, 65.2, 34.7, 26.7, 26.5, 26.2, 19.2, 14.3; HRMS (ESI): *m*/*z* calculated for $C_{26}H_{36}NaO_5Si$: $[M + Na]^+$ 479.2224, found 479.2268.

((*R*)-2-((3a*R*,5*R*,6*S*,6a*R*)-6-Azido-2,2-dimethyl tetrahydrofuro-[2,3-*d*][1,3]dioxol-5-yl)propoxy)(*tert*-butyl) diphenylsilane (12). A mixture of **11** (3.7 g, 8.1 mmol), triphenylphosphine (4.2 g, 16.2 mmol), and tri-iodoimidazole (3.6 g, 8.1 mmol) in toluene (50 mL) was stirred under reflux at a bath temperature of 120 °C for 4 h, after which additional triphenylphosphine (4.2 g, 16.2 mmol) and tri-iodoimidazole (3.6 g, 8.1 mmol) were added. After 24 h, the reaction mixture was cooled to rt, quenched with water (20 mL) and extracted with EtOAc (2 × 30 mL). The combined organic layers were washed with water, dried (Na_2SO_4), and evaporated under reduced pressure to provide a viscous oil which was directly used for the next step without further purification.

To a solution of the iodide (prepared above) in DMF (40 mL) was added sodium azide (1.5 g, 24.3 mmol) and the mixture was heated at 110 °C for 24 h. After cooling to room temperature, water (3 mL) was added to the solution, and the mixture was extracted with chloroform (3 × 25 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure. The residue was purified by flash column chromatography (EtOAc/pet. ether 1 : 10) to give azide **12** (2.53 g, 65% for two steps).

$[\alpha]_D^{25}$ = −34.84 (*c* = 0.6, $CHCl_3$); IR (neat): ν_{max} 2929, 2859, 1729, 1463, 1085, 1027, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.73–7.65 (m, 4H), 7.42–7.35 (m, 6H), 5.88 (d, *J* = 3.7 Hz, 1H), 4.69 (d, *J* = 3.7 Hz, 1H), 4.33–4.26 (dd, *J* = 3.0, 10.5 Hz, 1H), 3.93–3.87 (dd, *J* = 3.7, 9.8 Hz, 1H), 3.79 (d, *J* = 3.0 Hz, 1H), 3.68–3.61 (dd, *J* = 2.2, 9.8 Hz, 1H), 2.05–1.91 (m, 1H), 1.48 (s, 3H), 1.35 (s, 3H), 1.12 (d, *J* = 6.7 Hz, 3H), 1.07 (s, 9H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.7, 135.6, 133.7, 133.4, 129.5, 129.4, 127.8, 127.5, 125.7, 111.7, 104.3, 83.4, 79.9, 66.2, 65.2, 35.4, 26.8, 26.3, 26.2, 19.3, 13.5; HRMS (ESI): *m*/*z* calculated for $C_{26}H_{35}N_3NaO_4Si$: $[M + Na]^+$ 504.2289, found 504.2327.

(2*R*,3*S*,4*R*,5*R*)-3-Azido-6-(*tert*-butyldiphenylsilyloxy)-1,1-bis-(ethylthio)-5-methylhexane-2,4-diol (13). To a solution of azide **12** (2.5 g, 5.2 mmol) and ethanethiol (0.96 g, 15.6 mmol) in anhydrous dichloromethane (25 mL) was added $BF_3{\cdot}OEt_2$ (2.2 g, 15.6 mmol) at 0 °C under nitrogen atmosphere. After stirring the mixture at room temperature for 1 h, the reaction was quenched with saturated $NaHCO_3$ (10 mL) and the mixture was extracted with dichloromethane (3 × 25 mL). The extracts were combined, dried (Na_2SO_4), filtered, and the

filtrate evaporated *in vacuo*. The residue obtained was purified by flash chromatography on silica gel using pet. ether–EtOAc (2 : 1) gave diol **13** (2.1 g, 74%).

$[\alpha]_D^{25}$ = −26.13 (*c* = 0.45, $CHCl_3$); IR (neat): ν_{max} 3495, 2983, 2820, 2197, 1097, 665 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 7.70–7.62 (m, 4H), 7.47–7.34 (m, 6H), 4.10–4.05 (m, 2H), 4.00–3.94 (m, 1H), 3.91–3.81 (m, 2H), 3.71–3.60 (m, 2H), 3.52 (d, *J* = 1.5 Hz, 1H), 2.80–2.66 (m, 4H), 2.19–2.05 (m, 1H), 1.36–1.25 (m, 6H), 1.07 (s, 9H), 0.93 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.5, 132.7, 129.9, 127.8, 127.5, 78.0, 75.2, 68.4, 62.9, 55.0, 37.4, 29.6, 26.8, 25.7, 24.8, 19.1, 14.5, 13.3; HRMS (ESI): *m*/*z* calculated for $C_{27}H_{41}N_3O_3NaS_2Si$: $[M + Na]^+$ 570.2250, found 570.2240.

(5*R*,6*S*,7*R*,8*R*)-6-Azido-5-(bis(ethylthio)methyl)-7-(*tert*-butyldimethylsilyloxy)-2,2,3,3,8,12,12-heptamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecane (14). To a stirred solution of compound **13** (1.5 g, 2.74 mmol) in CH_2Cl_2 (20 mL) were added DIPEA (2.4 mL, 13.7 mmol) and TBSOTf (1.8 g, 6.8 mmol) sequentially at 0 °C under N_2 atmosphere. After 5 min, the reaction mixture was warmed to rt and stirred for 1 h. Then the reaction was quenched with saturated NH_4Cl solution and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed successively with water (10 mL), brine (10 mL), dried over Na_2SO_4 and concentrated under vacuum. The residue was purified by silica gel column chromatography (5% EtOAc/pet. ether) to afford **14** (1.9 g, 92%) as a colorless liquid.

$[\alpha]_D^{25}$ = +18.51 (*c* = 0.55, $CHCl_3$); IR (neat): ν_{max} 2930, 2858, 2107, 1466, 1255, 1107, 833, 701, 614 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.68–7.63 (m, 4H), 7.44–7.34 (m, 6H), 4.15–4.12 (dd, *J* = 3.0, 6.4 Hz, 1H), 3.90 (t, *J* = 4.2 Hz, 1H), 3.85 (d, *J* = 2.9 Hz, 1H), 3.80–3.76 (dd, *J* = 5.2, 10.2 Hz, 1H), 3.74–3.71 (dd, *J* = 4.2, 6.4 Hz, 1H), 3.60–3.55 (dd, *J* = 7.0, 10.2 Hz, 1H), 2.71–2.58 (m, 4H), 2.05–1.95 (m, 1H), 1.24 (t, *J* = 7.3 Hz, 3H), 1.18 (t, *J* = 7.4 Hz, 3H), 1.08 (d, *J* = 7.0 Hz, 3H), 1.06 (s, 9H), 0.95 (s, 9H), 0.82 (s, 9H), 0.22 (s, 3H), 0.18 (s, 3H), 0.09 (s, 3H), 0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 135.6, 133.7, 133.6, 129.5, 127.6, 75.7, 74.1, 66.5, 65.1, 55.9, 40.4, 29.7, 26.9, 26.3, 26.1, 26.0, 25.0, 19.2, 18.5, 18.3, 14.4, 14.3, 13.9, −3.7, −3.8, −4.1, −4.4; HRMS (ESI): *m*/*z* calculated for $C_{39}H_{69}N_3O_3NaS_2Si_3$: $[M + Na]^+$ 798.3980, found 798.3995.

Benzyl (5*R*,6*S*,7*R*,8*R*)-5-(bis(ethylthio)methyl)-7-(*tert*-butyldimethylsilyloxy)-2,2,3,3,8,12,12-heptamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecan-6-ylcarbamate (5). To a stirred solution of azide **14** (1.8 g, 2.3 mmol) and ammonium chloride (0.3 g, 5.8 mmol) in ethyl alcohol (18 mL) and water (6 mL), zinc powder (0.2 g, 3.0 mmol) was added and the mixture was stirred vigorously at room temperature. After 1 h (monitored by TLC), the mixture was diluted with ethyl acetate (25 mL). The reaction mixture was filtered through a pad of Celite, and washed with ethyl acetate (20 mL). The filtrate was washed with brine, dried over Na_2SO_4, and concentrated to give the amine product which was used without further purification for the subsequent reaction.

To a stirred solution of the above crude amine (1.6 g, 2.1 mmol) in CH_2Cl_2 (50 mL) was added DIPEA (0.7 mL, 4.2 mmol) followed by Cbz–Cl (50% in toluene, 0.8 mL, 2.5 mmol) at 0 °C. The reaction was warmed to rt and stirred for 1 h, quenched the reaction by the addition of water (20 mL) and the product was extracted with EtOAc (2 × 25 mL). The combined organic layer was dried over Na_2SO_4, filtered, concentrated and purified through silica gel chromatography (pet. ether) gave Cbz–amine **5** (1.6 g, 79% for two steps).

$[\alpha]_D^{25}$ = +9.1 (*c* = 0.4, $CHCl_3$); IR (neat): ν_{max} 3451, 2926, 2856, 1742, 1459, 1257, 1109, 1072, 699 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz): δ 7.68–7.61 (m, 4H), 7.43–7.30 (m, 10H), 7.29–7.18 (m, 1H), 5.12–4.99 (m, 3H), 4.39–4.33 (m, 1H), 3.95–3.92 (dd, *J* = 2.4, 6.8 Hz, 1H), 3.88–3.81 (m, 2H), 3.51–3.46 (dd, *J* = 6.8, 10.7 Hz, 1H), 2.76–2.53 (m, 4H), 1.95–1.87 (m, 1H), 1.27–1.15 (m, 6H), 1.06 (s, 9H), 1.05 (d, *J* = 7.3 Hz, 3H), 0.90–0.81 (m, 18H), 0.16 (s, 3H), 0.08–0.04 (m, 6H), −0.02 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.5, 135.67, 135.62, 133.8, 131.9, 129.5, 128.3, 128.0, 127.8, 127.6, 75.3, 71.9, 66.3, 65.7, 56.1, 53.7, 41.4, 29.7, 27.05, 27.00, 26.3, 26.03, 26.01, 19.1, 18.2, 14.46, 14.41, −5.9, −3.7, −3.9; HRMS (ESI): *m*/*z* calculated for $C_{47}H_{78}NO_5S_2Si_3$: $[M + H]^+$ 884.4623, found 884.4656.

Benzyl (5*R*,6*S*,7*R*,8*R*)-7-(*tert*-butyldimethylsilyloxy)-5-(4-methoxy-2-nitrobenzoyl)-2,2,3,3,8,12,12-heptamethyl-11,11-diphenyl-4,10-dioxa-3,11-disilatridecan-6-ylcarbamate (16). A solution of **5** (1.2 g, 1.3 mmol) in a mixture of acetone/water (20 mL, 9 : 1) was treated with $NaHCO_3$ (0.45 g, 5.4 mmol) and iodine (0.75 g, 3.0 mmol). After stirring at rt for 1 h, the suspension was diluted with an aqueous solution of $Na_2S_2O_3$ (20 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL) and the combined organic phases were dried (Na_2SO_4), filtered, concentrated and used directly for the next step.

To a stirred solution of 4-iodo 3-nitro anisole **4** (0.3 g, 1.1 mmol) in anhydrous ether (10 mL) at −40 °C was added PhMgCl (2 M in THF, 0.58 mL, 1.1 mmol) in dropwise. After 10 min, aldehyde (1.0 g, 1.2 mmol) in dry ether (10 mL) was added to the reaction mixture at −40 °C and stirred for another 1 h. The reaction mixture was quenched with saturated NH_4Cl (5 mL) and poured into water (20 mL). The aqueous phase was extracted with ethyl acetate (2 × 25 mL) and the organic fractions were washed with brine (20 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Flash chromatography on silica gel furnished the product **15** (0.73 g, 58% for two steps) as colorless oil.

Dess–Martin periodinane (0.37 g, 0.89 mmol) was added at 0 °C under nitrogen to a solution of alcohol **15** (0.69 g, 0.74 mmol) in CH_2Cl_2 (15 mL) and the resulting mixture was stirred at rt for 3 h. After completion of the reaction (TLC analysis), saturated $NaHCO_3/Na_2S_2O_3$ solution (1 : 1, 20 mL) was added, the aqueous phase was separated and extracted with CH_2Cl_2 (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4, filtered and concentrated. Purification of the residue by flash chromatography gave ketone **16** (0.63 g, 92%) as colorless oil.

$[\alpha]_D^{25}$ = +89.81 (*c* = 2.16, $CHCl_3$); IR (neat): ν_{max} 2931, 2857, 1723, 1608, 1539, 1464, 1253, 1076, 834, 700.6, 613 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz): δ 8.23 (d, *J* = 8.8 Hz, 1H), 7.65–7.54

(m, 4H), 7.47–7.31 (m, 11H), 7.19 (d, J = 2.4 Hz, 1H), 7.11–7.06 (dd, J = 2.4, 8.7 Hz, 1H), 7.03–6.92 (m, 1H), 5.28–5.20 (m, 2H), 5.12 (t, J = 11.1 Hz, 1H), 4.43–4.28 (m, 1H), 4.08–4.03 (m, 1H), 3.89 (s, 3H), 3.62–3.53 (dd, J = 6.4, 10.2 Hz, 1H), 3.37–3.28 (dd, J = 7.7, 8.1 Hz, 1H), 2.12–1.94 (m, 1H), 1.00 (s, 9H), 0.95–0.88 (m, 12H), 0.86 (s, 9H), 0.16 (s, 3H), 0.13 (s, 3H), 0.06 (s, 3H), 0.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 198.0, 161.8, 156.1, 150.7, 136.4, 135.4, 133.6, 132.6, 130.2, 129.46, 129.42, 128.5, 128.4, 128.0, 127.8, 127.5, 127.2, 123.5, 116.6, 110.0, 78.2, 70.3, 66.8, 65.7, 55.9, 53.9, 41.0, 26.6, 25.9, 25.5, 19.0, 18.0, 17.9, 12.3, −4.1, −4.5, −5.0; HRMS (ESI): m/z calculated for $C_{50}H_{73}N_2O_9Si_3$: $[M + H]^+$ 929.4618, found 929.4628.

Benzyl (5*R*,6*S*,7*R*)-5-((*R*)-1-hydroxypropan-2-yl)-7-(4-methoxy-2-nitrobenzoyl)-2,2,3,3, 9,9,10,10-octamethyl-4,8-dioxa-3,9-disilaundecan-6-ylcarbamate (17). To a stirred solution of **16** (0.55 g, 0.59 mmol) in MeOH (5 mL) was added NH_4F (43.0 mg, 1.18 mmol) at 0 °C. After complete consumption of starting material (~4 h, by TLC analysis), methanol was evaporated and EtOAc (20 mL) was added. The organic layer was washed with aqueous $NaHCO_3$ solution (2 × 20 mL), water and brine sequentially, dried over Na_2SO_4 and concentrated under reduced pressure. The obtained residue was purified by silica gel column chromatography (pet. ether–EtOAc (3 : 1)) to give alcohol **17** (335 mg, 82%) as viscous oil.

$[\alpha]_D^{25}$ = +53.8 (c = 0.06, $CHCl_3$); IR (neat): ν_{max} 3435, 2930, 2861, 1696, 1639, 1524, 683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.48–7.30 (m, 7H), 7.00–6.96 (dd, J = 2.5, 8.4 Hz, 1H), 5.16–4.98 (m, 3H), 4.70 (d, J = 4.2 Hz, 1H), 4.30–4.23 (m, 1H), 3.91–3.84 (m, 4H), 3.64–3.57 (dd, J = 7.5, 10.9 Hz, 1H), 3.38–3.32 (dd, J = 4.2, 10.9 Hz, 1H), 1.87–1.79 (m, 1H), 0.93–0.81 (m, 21H), 0.12–0.04 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 199.8, 161.5, 156.1, 148.4, 136.5, 131.6, 131.3, 128.4, 128.2, 128.0, 125.4, 118.9, 109.4, 76.9, 73.3, 66.8, 64.0, 56.0, 54.6, 38.6, 25.9, 25.8, 18.0, 14.5, −4.0, −4.3, −4.6, −5.0; HRMS (ESI): m/z calculated for $C_{34}H_{54}O_9N_2NaSi_2$: $[M + Na]^+$ 713.3260, found 713.3268.

(2*S*,3*R*,4*S*,5*R*)-4-(Benzyloxycarbonylamino)-3,5-bis(*tert*-butyldimethyl-silyloxy)-6-(4-methoxy-2-nitrophenyl)-2-methyl-6-oxohexanoic acid (3). BAIB (280 mg, 0.87 mmol) and TEMPO (4.5 mg, 0.03 mmol) were added sequentially to a stirred solution of alcohol **17** (200 mg, 0.29 mmol) in acetonitrile (pH = 7 buffer solution, 3 : 1, 10 mL) at rt and stirred for 6 h. The reaction was quenched by the addition of saturated $Na_2S_2O_3$ solution (10 mL) and then diluted with Et_2O (30 mL). The separated organic phase was washed with saturated aqueous $NaHCO_3$, brine, dried and concentrated under reduced pressure. The residue was purified by column chromatography to yield the pure acid **3** (159 mg, 78%) as clear oil.

$[\alpha]_D^{25}$ = +82.4 (c = 0.94, $CHCl_3$); IR (neat): ν_{max} 3440, 2934, 2858, 1715, 1535, 1251, 1125, 837, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.68 (d, J = 8.4 Hz, 1H), 7.41–7.31 (m, 6H), 7.08–7.02 (dd, J = 2.4, 8.6 Hz, 1H), 5.12 (d, J = 9.8 Hz, 1H), 5.07 (s, 2H), 4.72 (d, J = 4.9 Hz, 1H), 4.27–4.18 (m, 1H), 4.03 (t, J = 4.7 Hz, 1H), 3.89 (s, 3H), 2.75–2.65 (m, 1H), 1.13 (d, J = 7.1 Hz, 3H), 0.87 (s, 9H), 0.84 (s, 9H), 0.11–0.02 (m, 12H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 198.4, 177.8, 161.8, 155.9, 149.4, 136.4, 132.1, 128.4, 128.2, 128.1, 124.4, 118.0, 109.8, 72.2, 67.0, 56.0, 55.1, 43.6, 25.8, 25.7, 18.1, 18.0, 13.5, −4.0, −4.5, −4.6, −5.0; HRMS (ESI): m/z calculated for $C_{34}H_{52}O_{10}N_2NaSi_2$: $[M + Na]^+$ 727.3052, found 727.3054.

Conclusions

In conclusion, this sequence of chemical transformations starting from D-glucose in a linear high yielding process with affordable chemicals provided differentially protected unusual amino acid (ADMOA, **3**) present in solomonamide A in multigram quantities in very efficient manner.

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21 The present route has an advantage of using the cheaply available starting material, D-glucose, when compared to our earlier method using expensive (*R*)-Roche ester as the starting material (ref. 9). Even though, the numbers of synthetic transformations are high the present method offers operational simplicity.
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