The enantioselective synthesis of APTO and AETD: polyhydroxylated β-amino acid constituents of the microsclerodermin cyclic peptides†

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The polyhydroxylated β-amino acids (2*S*,3*R*,4*S*,5*S*,7*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid (APTO) and (2*S*,3*R*,4*S*,5*S*,7*E*,9*E*)-3-amino-10-(4-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid (AETD) are key components of the microsclerodermin family of anti-fungal cyclic peptides. They have been synthesised in protected form in twelve steps using a unified strategy, with the introduction of the unsaturated sidechain in the final step of the synthesis from a common aldehyde intermediate. The synthesis features the ordered application of asymmetric aminohydroxylation and dihydroxylation reactions to efficiently introduce the stereochemistry of the targets with high selectivity.

Introduction

The microsclerodermins are a family of cyclic hexapeptides isolated from marine sponges of the *Microscleroderma* and *Theonella* genera in waters off New Caledonia and the Philippines.[1] Nine members of this natural product family, microsclerodermins A–I, have been isolated to date and all exhibit anti-fungal activity against the clinically significant fungal pathogen *Candida albicans* in a paper disc diffusion assay. In addition, microsclerodermins F–I display moderate cytotoxicity against the HCT-116 cell line (1.0–2.4 μg mL^{-1}).[1]

Structurally, members of the family are typified by microsclerodermin C (**1**, Fig. 1), which contains a 23-membered ring constructed of six amino acid residues. Three of these, glycine, *N*-methylglycine and (3*R*)-4-amino-3-hydroxybutyric acid (GABOB) are common to all members of the microsclerodermin family. The remaining three unusual amino acids display considerable variation across the microsclerodermin family and for microsclerodermin C consist of (*R*)-*N*-carbamoyl-6-chlorotryptophan, [(2*R*,3*S*)-3-amino-2-hydroxy-5-oxo-2-pyrrolidin-2-yl]-acetic acid and (2*S*,3*R*,4*S*,5*S*,7*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid (APTO).

The synthetic challenge posed by the microsclerodermins combined with their significant biological activity has made them an attractive target for total synthesis. A key issue for any projected total synthesis is the efficient construction of the unusual amino acids and in particular the 3-amino-2,4,5-trihydroxyacid typified by APTO in microsclerodermin C. Without exception, the congeners of APTO contain the same 3-amino-2,4,5-trihydroxyalkanoic acid head group but vary in the nature of the aromatic terminated sidechain.

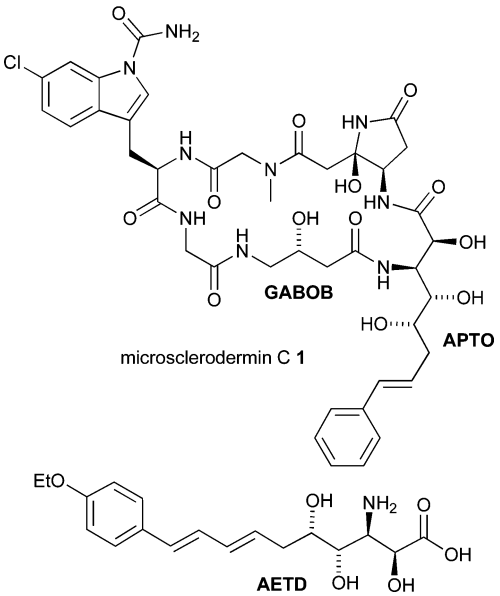

Fig. 1 Microsclerodermin C **1** and AETD.

A number of synthetic studies targeting the microsclerodermins have appeared to date. Foremost among these reports is the total synthesis of microsclerodermin E by Zhu and Ma in 2003.[2] This group developed an enantiospecific 21-step synthesis of a protected AETD–GABOB dipeptide fragment wherein the stereochemistry of the head group was derived from δ-gluconolactone.

Synthetic studies targeting the 3-amino-2,4,5-trihydroxy acid component of the microsclerodermins have also been reported. These include the pioneering work of Shioiri and co-workers[3] who completed a 31-step enantiospecific synthesis of the 3-amino-2,4,5-trihydroxy acid component of microsclerodermins A and B, (2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-amino-12-(4-methoxyphenyl)-6-methyl-2,4,5-trihydroxydodec-11-enoic acid (AMMTD), from methyl (*R*)-(−)-3-hydroxy-2-methylpropionate. Recently, Chandrasekhar and Sultana[4] have reported the 26-step enantiospecific synthesis of AMMTD from (*S*)-(−)-citronellal as starting

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† Electronic supplementary information (ESI) available: General experimental details together with experimental procedures and spectroscopic data for compounds **4–9**, **16–21**, **23–27** and copies of ^{1}H and ^{13}C NMR spectra for (7*E*)-**2**, and (7*E*,9*E*)-**3**. See DOI: 10.1039/b707891a

material. Herein we disclose the efficient enantioselective synthesis of 3-amino-2,4,5-trihydroxy acid components of microscleroderdermins C and D (APTO) and microsclerodermin E (AETD) in protected form.

Results and discussion

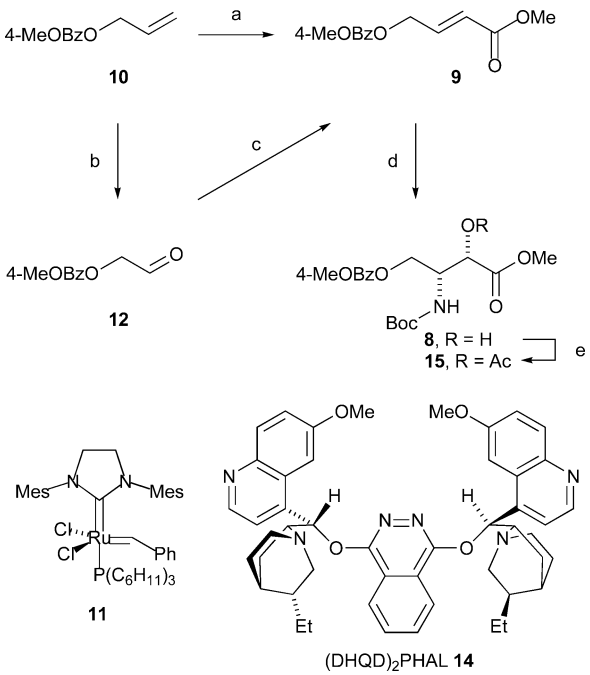
On consideration of the target structures, it was envisaged that protected APTO **2** and AETD **3** (Scheme 1) could be derived from a common, aldehyde intermediate **4** in a single step, by Wittig olefination with an appropriate phosphonium salt. Aldehyde **4** could be derived from diol **5** in three steps: protection of the C4–C5 diol as the acetonide, oxidative deprotection of the *p*-methoxyphenyl protecting group and oxidation of the resulting alcohol to the aldehyde. Diol **5** could in turn be formed from (*E*)-alkene **6** by Sharpless asymmetric dihydroxylation (AD). The diastereoselectivity of this key transformation would depend on effective stereochemical induction from the AD catalyst and any induction derived from the chiral substrate.

(*E*)-Alkene **6** could be obtained by modified Julia olefination of aldehyde **7**, which could in turn be prepared from β-amino alcohol **8**. Finally, it was envisaged that β-amino alcohol **8** could be constructed with high enantioselectivity from (*E*)-alkene **9** by Sharpless asymmetric aminohydroxylation (AA), wherein careful matching of substrate and catalyst controls the enantio- and regioselectivity of the reaction.

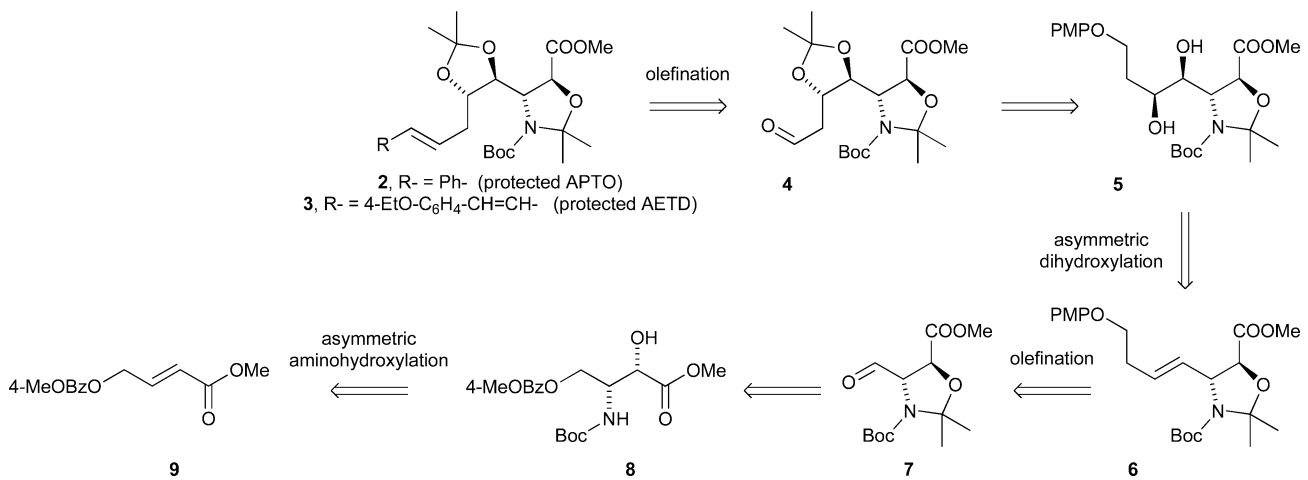
This strategy allows for the synthesis of both unusual amino acids APTO **2** and AETD **3** from aldehyde **4** through introduction of the unsaturated sidechain in the final step of the synthesis. The synthesis also features a carefully orchestrated sequence of Sharpless AA and AD reactions to efficiently install the polyhydroxylated amino acid functionality present in APTO, AETD and other common amino acid building blocks of the microsclerodermin family.[1]

Two synthetic routes were developed for the synthesis of the (*E*)-alkene substrate required for the substrate directed AA reaction (Scheme 2). Cross metathesis of allyl 4-methoxybenzoate **10**[5] and methyl acrylate using Grubbs' second generation catalyst **11**[6] selectively afforded (*E*)-alkene **9** in 65% yield. Although this process was efficient on a small scale, the need for substantial quantities of (*E*)-alkene **9** demanded the development of a more cost effective alternative. Oxidative cleavage of allyl ester **10** gave aldehyde **12**[7] in quantitative yield which was used directly in a Horner–Wadsworth–Emmons reaction with methyl diethylphosphonoacetate **13** to give the products with an *E* : *Z* ratio of 25 : 1. Separation of the diastereomers was readily achieved by flash chromatography to afford pure (*E*)-alkene **9** in 91% yield over two steps.

The (DHQD)$_2$PHAL **14** mediated AA reaction[8] of (*E*)-alkene **9** proceeded smoothly to afford β-amino alcohol **8** as a single



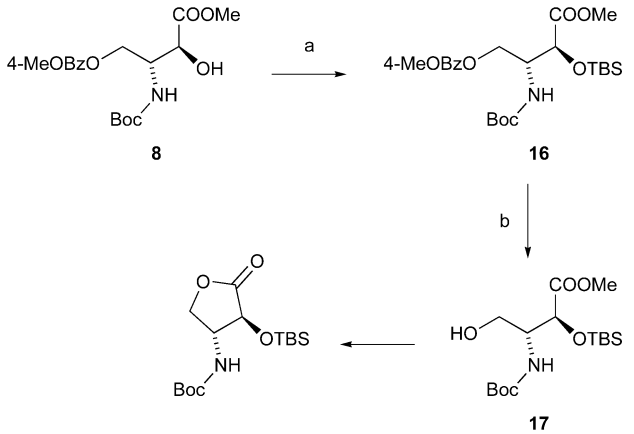
Scheme 2 (a) CH_2=CHCOOMe, Grubbs' second generation catalyst **11** (7 mol%), CH_2Cl_2, Δ, 36 h, 65%; (b) OsO_4 (1 mol%), $NaIO_4$, Et_2O, H_2O, rt, 39 h; (c) $(EtO)_2POCH_2COOMe$ **13**, *n*-BuLi, THF, −78 °C to rt, 5 h, 91% over two steps; (d) *t*-$BuOCONH_2$, $K_2OsO_2(OH)_4$ (5 mol%), (DHQD)$_2$PHAL **14** (7 mol%), 1,3-dichloro-5,5-dimethylhydantoin, NaOH, *n*-PrOH, H_2O, rt, 48 h, 84%; (e) Ac_2O, Et_3N, 4-(dimethylamino)pyridine, CH_2Cl_2, rt, 1 h, 40%.



Scheme 1 Retrosynthetic analysis.

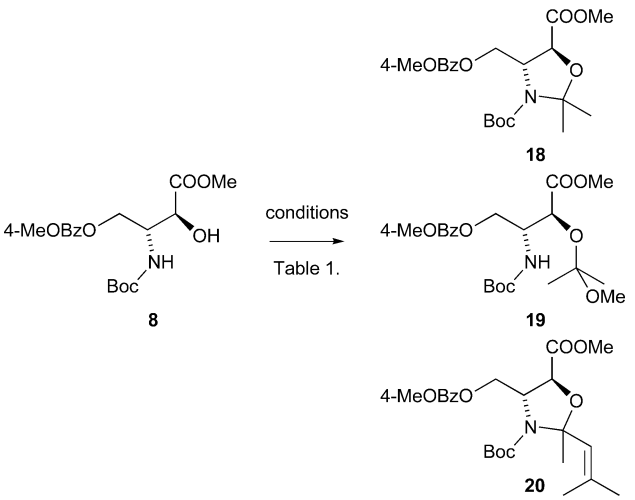
regioisomer in 84% yield and 97% enantiomeric excess as determined by chiral HPLC of the acetate derivative **15**.[9] The (*S*)-absolute configuration of the secondary alcohol bearing C2 stereocentre was established by the modified Mosher's method[10] and was consistent with the outcome predicted by the Sharpless mnemonic.[8] The high regioselectivity obtained in this AA reaction derives from the high levels of substrate direction afforded by 4-methoxybenzoate ester protection of the adjacent allylic alcohol functionality.[5,7]

With β-amino alcohol **8** in hand two avenues for the elaboration to AD substrate **6** were explored. Initially, protection of secondary alcohol **8** gave silyl ether **16** in 75% yield and transesterification of the 4-methoxybenzoate ester protecting group gave primary alcohol **17** in 64% yield (Scheme 3). Despite the success of this sequence, attempted oxidation of alcohol **17** by a range of methods[11] failed to give the desired aldehyde required for the Julia olefination and instead gave decomposition to a range of unidentified products. Alcohol **17** was also observed to undergo lactonisation on prolonged storage.



Scheme 3 (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, −78 °C to rt, 22 h, 75%; (b) Cs_2CO_3, MeOH, rt, 24 h, 64%.

In an effort to overcome these difficulties the protection of β-amino alcohol **8** as the oxazolidine derivative **18** was explored (Scheme 4, Table 1). In addition to protecting both amine and alcohol functional groups, it was anticipated that the *trans* relationship of the ester and alcohol functional groups in this cyclic derivative would eliminate the propensity for lactone formation. The protection of alcohol **8** to give oxazolidine **18** proved difficult under a range of conditions.[12] The use of excess 2,2-dimethoxypropane (2,2-DMP) and *p*-toluenesulfonic acid (TsOH) (Table 1, entry 1) gave mixtures of starting alcohol **8**, intermediate



Scheme 4

acetal **19** and product **18**. The use of 2-methoxypropene (2-MP) at lower temperature (entry 2) also failed to give full conversion. The use of 2-methoxypropene and pyridinium *p*-toluenesulfonate (PPTS) at elevated temperature (entry 3) gave complete conversion and an improved yield of oxazolidine **18** but also afforded condensation by-product **20** as a single diastereomer of undetermined configuration. Finally, it was discovered that reaction of alcohol **8** at room temperature for 2 h gave clean conversion to intermediate acetal **19**, after which, the volatile components were removed from the reaction mixture on a rotary evaporator and oxazolidine formation was promoted by heating the remaining toluene solution. In this manner oxazolidine **18** was formed in 84% yield with a small amount of amino alcohol **8** (15%) being recovered.

Transesterification of the 4-methoxybenzoate ester **18** with caesium carbonate gave an 81% yield of primary alcohol **21** (Scheme 5). This was oxidised to aldehyde **7** in quantitative yield using Dess–Martin periodinane,[13] setting the stage for the Julia olefination chain extension.

Both benzothiazol-2-yl (BT)[14] and 1-phenyl-1*H*-tetrazol-5-yl (PT)[15] sulfones were synthesised in order to evaluate the influence of the aromatic substituent on the selectivity of the modified Julia olefination reaction.[16] The synthesis started with mono-protected propanediol **22**[17] (Scheme 6). In each case, formation of the thioether was achieved under Mitsunobu conditions[18] followed by molybdenum(VI) mediated oxidation[19] to give the corresponding sulfones **23** and **24**.

Julia olefination using BT-sulfone **23** (Table 2, entry 1) or PT-sulfone **24** (entry 2) and lithium diisopropylamide (LDA) as the

Table 1 Conditions for oxazolidine formation

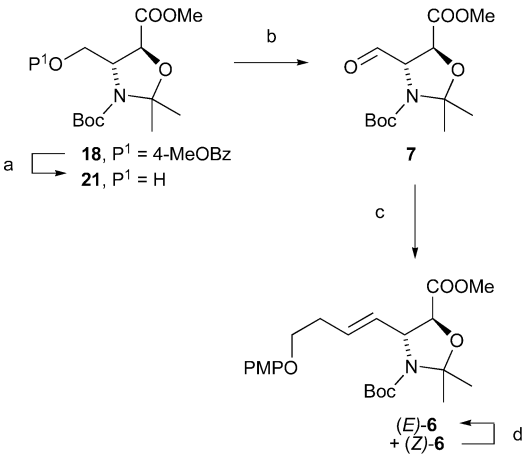
					Yield (%)			
Entry	Reagent	Acid	Solvent	Temp./°C (time/h)	**8**	**18**	**19**	**20**
1	2,2-DMP	TsOH	Benzene	95 (32)	40	36	2	—
2	2-MP	TsOH	Benzene	0 (2), rt (5)	22	60	—	—
3	2-MP	PPTS	Toluene	rt (1), 110 (3)	—	77	—	20
4[a]	2-MP	PPTS	Toluene	rt (2), 110 (3)	15	84	—	—

[a] Low boiling volatile components were removed on a rotary evaporator prior to heating the reaction mixture.

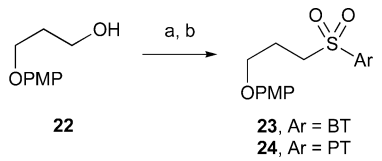
Table 2 Julia olefination of aldehyde **7** with sulfones **23** and **24**

Entry	Sulfone	Solvent	Base	Temp./°C	Time/h	Yield (%)	$E : Z^a$
1	**23**	THF	LDA	−78	17	42	1.2 : 1
2	**24**	THF	LDA	−78	17	35	1.6 : 1
3	**24**	1,2-DME	NaHMDS	−60	0.5	58	1.8 : 1
4	**24**	1,2-DME	KHMDS	−60	0.75	67	2.7 : 1

[a] Determined by integration of the C3-H signals in the 200 MHz ^{1}H NMR spectrum of the crude reaction mixture.



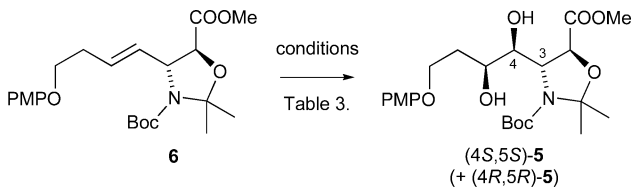
Scheme 5 (a) Cs_2CO_3, MeOH, rt, 16 h, 81%; (b) Dess–Martin periodinane, CH_2Cl_2, rt, 1 h, quant.; (c) **23** or **24**; then base (see Table 2); (d) PhSH, AIBN, benzene, 85 °C, 10 days, 98%, $E : Z$ 6.5 : 1.



Scheme 6 (a) ArSH, PPh_3, THF, diisopropyl azodicarboxylate, 0 °C to rt, Ar = BT, 15 h, 82%, Ar = PT, 2.5 h, 69%; (b) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 0 °C to rt, Ar = BT, 30 h, 98%, Ar = PT, 20 h, 99%.

base under Barbier conditions[16] gave alkene **6** in modest yields and selectivities. The PT-sulfone was found to most strongly favour formation of the (*E*)-alkene. The effect of solvent polarity and base counter-ion on the selectivity of the reaction was studied using the more polar solvent 1,2-dimethoxyethane (1,2-DME) in conjunction with sodium bis(trimethylsilyl)amide (NaHMDS, entry 3) or potassium bis(trimethylsilyl)amide (KHMDS, entry 4). The results were in agreement with previous studies[16] with the most (*E*)-selective conditions being 1,2-DME with KHMDS. The highest yield was also obtained under these conditions. Despite the modest selectivity of the modified Julia olefination, it was discovered that alkene mixtures enriched in (*Z*)-alkene (*Z*)-**6** could be successfully isomerised to the (*E*)-alkene isomer (*E*)-**6** using phenylthiyl radical.[20]

With quantities of the (*E*)-alkene (*E*)-**6** in hand, the AD reaction[21] to install the 4,5-diol functionality was investigated (Scheme 7). It was envisaged that the diastereoselectivity of this reaction would be governed by both the influence of the resident stereocentres within the substrate and the control imparted by the chiral ligands of the dihydroxylation catalyst. The intrinsic diastereoselectivity imparted by the substrate was determined by performing the reaction in the absence of chiral ligand (Table 3, entry 1); this favoured the (4*S*,5*S*)-product (4*S*,5*S*)-**5** in a modest 2 : 1 ratio of diastereomers as determined by ^{1}H NMR integration of the C2-H and C3-H signals.[22] This modest preference for the 3,4-*anti* diastereomer was consistent with previous reports regarding the dihydroxylation of *N*-*tert*-butoxycarbonyl-2,2-dimethyloxazolin-3-yl substituted olefins.[23]



Scheme 7

Table 3 Diastereoselective dihydroxylation of alkene **6**

Entry	Temperature/°C (time/h)	Ligand	Yield (%)	(4*S*,5*S*) : (4*R*,5*R*)[a]
1[b]	28 (2)	none	48	2.0 : 1
2[c]	0 (5), 28 (72)	$(DHQ)_2PHAL$	0	n/a
3[c]	0 (5), 28 (72)	$(DHQD)_2PHAL$	0	n/a
4[d]	17 (17)	DHQ–CLB	11	3.3 : 1
5[d]	17 (17)	DHQD–CLB	5	1 : 2.5
6[d]	17 (17)	DHQ–IND	42	7.4 : 1
7[d]	17 (17)	DHQD–IND	19	1 : 5.1
8[d]	17 (10), 27 (4)	DHQ–IND	85	7.4 : 1

[a] Determined by integration of the C2-H and C3-H signals in the 300 MHz ^{1}H NMR spectrum of the crude reaction mixture. [b] OsO_4 (10 mol%), *N*-methylmorpholine-*N*-oxide (3.2 eq.), THF–*t*-BuOH–H_2O. [c] AD-mix-α (entry 2) or AD-mix-β (entry 3),[21] $MeSO_2NH_2$ (1.0 eq.), $NaHCO_3$ (3.0 eq.), *t*-BuOH–H_2O. [d] $K_2OsO_2(OH)_4$ (1 mol%), ligand (6 mol%), $K_3Fe(CN)_6$ (3.0 eq.), K_2CO_3 (3.2 eq.), $NaHCO_3$, (3.2 eq.), $MeSO_2NH_2$ (3.2 eq.), *t*-BuOH–H_2O.

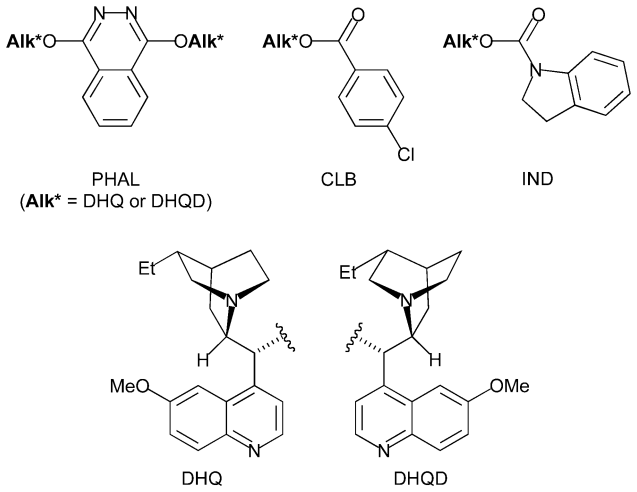


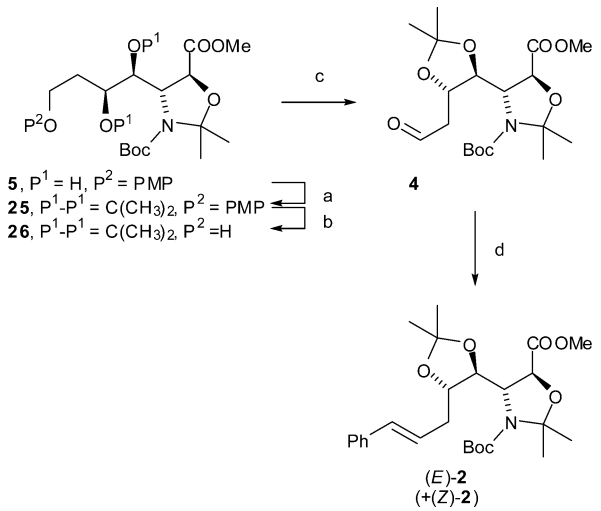
Fig. 2 Sharpless ligands.

Dihydroxylation with the phthalazine-derived chiral ligands $(DHQ)_2PHAL$ (Fig. 2) and $(DHQD)_2PHAL$ **14** failed to afford the desired product, instead leading to slow formation of a polar compound consistent with base mediated hydrolysis of the methyl ester to a carboxylic acid. The low reactivity of the alkene was presumed to be due to the large steric demands imposed by the proximal *N*-(*tert*-butoxycarbonyl)-2,2-dimethyloxazoline ring system, which prevented effective interaction with the catalyst.

To overcome this problem sterically less demanding mono-alkaloid ligands were investigated. Although these have been found to typically provide lower levels of catalyst derived stereocontrol in the AD reaction,[21] it was anticipated that matching the stereocontrol of the ligand and substrate would increase the modest preference for the (4*S*,5*S*)-diastereomer (4*S*,5*S*)-**5** observed above.[24] Asymmetric dihydroxylation reaction with the mono-alkaloid ligand DHQ–CLB gave a modest increase in selectivity for the desired diastereomer (entry 4). Conversely, the pseudo-enantiomeric DHQD–CLB ligand overturned the substrate bias to favour the (4*R*,5*R*)-diastereomer (entry 5). The use of the mono-alkaloid ligand DHQ–IND gave a 7.4 : 1 ratio favouring the desired (4*S*,5*S*)-diastereomer in a matched reaction (entry 6), which was overturned by the DHQD–IND ligand (entry 7). On a larger scale, it was observed that higher yields could be obtained through the use of elevated temperature providing an 85% yield of the diols, favouring the (4*S*,5*S*)-diastereomer, with no loss of diastereoselectivity. The diastereomers produced by the dihydroxylation reaction were inseparable by column chromatography so the mixture was carried through the remaining steps and separated at the conclusion of the synthesis.

The successful application of the AA followed by AD sequence for the synthesis of the protected 3-amino-2,4,5-trihydroxy acid head group of APTO and AETD is noteworthy. In the synthesis of AMMTD reported by Chandrasekhar and Sultana[4] the alternative sequence of AD followed by AA reaction was attempted to construct a closely related stereochemical array. In this case the AA reaction failed to provide the desired product and necessitated a lengthy synthetic detour to install the required functionality. The failure of the AA reaction in this context can be explained given the generally lower substrate tolerance of the AA reaction when compared to its AD counterpart.[8,21]

Protection of diol **5** to give acetonide **25** proceeded smoothly (99%) and oxidative deprotection of the PMP ether then afforded primary alcohol **26** in 95% yield (Scheme 8). Oxidation[13] afforded aldehyde **4**, which was used without purification in the subsequent step.

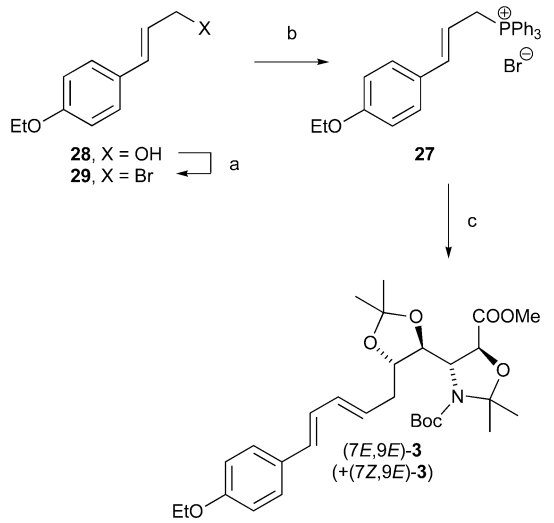


Scheme 8 (a) 2,2-DMP, CH_2Cl_2, (1*S*)-(+)-10-camphorsulfonic acid, 35 min, 99%; (b) $(NH_4)_2Ce(NO_3)_6$, CH_3CN, H_2O, 0 °C, 18 min, 95%; (c) Dess–Martin periodinane, CH_2Cl_2, rt, 45 min, quant.; (d) benzyltriphenylphosphonium chloride, KHMDS, benzene, 0 °C to rt, 15 min; then aldehyde **4**, benzene, 0 °C to rt, 1 h, 78%.

Wittig reaction of aldehyde **4** using the ylide derived from treatment of benzyltriphenylphosphonium chloride with potassium bis(trimethylsilyl)amide gave alkene **2** in 78% yield, in a 3.5 : 1 ratio of (7*E*) : (7*Z*)-diastereomers as determined by ^{1}H NMR integration of the C7-H and C8-H signals. The isomers were inseparable by flash chromatography. Preparative HPLC was used to separate the two major isomers and a mixed fraction containing trace by-products. The by-products were not analysed further but were assumed to be alkene products derived from the minor diastereomer formed in the AD reaction which were carried through the subsequent steps. The assigned (*E*)-stereochemistry of the major isomer (*E*)-**2** was consistent with the magnitude of the C7-H vicinal coupling constant ($^3J_{7,8}$ = 15.9 Hz). In contrast, a smaller C7-H vicinal coupling constant ($^3J_{7,8}$ = 11.7 Hz) was observed for the minor (7*Z*)-isomer (*Z*)-**2**. Protected APTO (*E*)-**2** was synthesised in twelve linear steps from allyl ester **10** in an overall yield of 12% and in 97% ee. With this target in hand the project turned to focus on the synthesis of protected AETD which contains the same polyhydroxylated amino acid core but differs in the unsaturated sidechain.

The phosphonium salt **27** required for the synthesis of protected AETD **3** was prepared in two steps from the known (*E*)-allylic alcohol **28** (Scheme 9).[25] Bromination using phosphorus tribromide afforded unstable allylic bromide **29** which was immediately treated with triphenylphosphine to give phosphonium salt **27** as a colourless hygroscopic solid.

The Wittig reaction with aldehyde **4** was conducted under analogous conditions to those developed for the synthesis of APTO derivative **2** and gave diene product **3** in 63% yield, with a 3.2 : 1 ratio of (7*E*,9*E*) : (7*Z*,9*E*) diastereomers as determined



Scheme 9 (a) PBr_3, diethyl ether, 0 °C to rt, 80 min, 89%; (b) PPh_3, benzene, rt, 15 h, 87%; (c) KHMDS, benzene, 0 °C to rt, 10 min; then aldehyde **4**, benzene, 0 °C to rt, 25 min, 63%.

by ^{1}H NMR integration of the C7-H signals. Preparative HPLC was used to separate the two major isomers and a mixed fraction containing trace by-products. The assigned (7*E*)-stereochemistry of the major isomer (7*E*,9*E*)-**3** was consistent with the magnitude of the C7-H vicinal coupling constant ($^3J_{7,8} = 14.8$ Hz). In contrast, a smaller C7-H vicinal coupling constant ($^3J_{7,8} = 10.9$ Hz) was observed for the minor (7*Z*)-isomer (7*Z*,9*E*)-**3**.

Conclusions

Protected APTO (*E*)-**2** and AETD (7*E*,9*E*)-**3** were synthesised in twelve linear steps from allyl ester **10** in an overall yield of 12% and 9% respectively and in 97% ee. The strategy allowed for the synthesis of both unusual amino acids from aldehyde **4** through the introduction of the unsaturated sidechain in the final step. This synthesis features a carefully orchestrated sequence of Sharpless AA and AD reactions to install the polyhydroxylated amino acid functionality present in these targets and which is common to other amino acid building blocks of the microsclerodermin family.

Experimental

(4*R*,5*S*)-3-*tert*-Butyl-5-methyl-4-{(4*S*,5*S*)-5-[(*E*)-3-phenylprop-2-enyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2,2-dimethyloxazolidine-3,5-dicarboxylate (7*E*)-2 and (4*R*,5*S*)-3-*tert*-butyl-5-methyl-4-{(4*S*,5*S*)-2,2-dimethyl-5-[(*Z*)-3-phenylprop-2-enyl]-1,3-dioxolan-4-yl}-2,2-dimethyloxazolidine-3,5-dicarboxylate (7*Z*)-2

To a suspension of benzyltriphenylphosphonium chloride (0.10 g, 0.26 mmol) in benzene (6.0 mL) at 0 °C was added a solution of potassium bis(trimethylsilyl)amide (0.50 M in toluene, 0.53 mL, 0.27 mmol). The bright orange solution was allowed to warm to room temperature for 15 min and was cooled to 0 °C. A solution containing a mixture of aldehyde (4*S*,5*S*)-**4** and aldehyde (4*R*,5*R*)-**4** [(4*S*,5*S*)-**4** : (4*R*,5*R*)-**4** = 7 : 1, 0.11 g, 0.27 mmol] in benzene (2.5 mL) was added. The brown solution was allowed to warm to room temperature and was stirred for 1 h. Dry methanol (4.0 mL) was added followed by ammonium chloride solution (sat. aq., 10 mL) and the crude product was extracted into ethyl acetate (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an orange residue (0.24 g). Flash chromatographic purification (20% ethyl acetate : hexanes) of the crude product gave an inseparable mixture of (7*E*)-alkene (7*E*)-**2** and (7*Z*)-alkene (7*Z*)-**2** as a viscous, clear colourless liquid (0.096 g, 78%); $[\alpha]_D^{19}$ −2.2 (*c* 1.7, CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 1763 (m), 1740 (m), 1701 (s, C=O); HRMS (+ESI) calc. for $C_{26}H_{37}O_7N$ + Na 498.2468, found 498.2458; *m*/*z* (+ESI) 498 ([M + Na]$^+$, 100%), 442 (24). Preparative HPLC purification (RTI Zorbax Sil, 7.5% ethyl acetate : hexanes) of a portion of the purified product (0.048 g) gave pure (7*E*)-alkene (7*E*)-**2** (t_R ≈31.5 min) as a viscous, clear, colourless liquid (0.038 g, 31%); $[\alpha]_D^{21}$ −3.1 (*c* 3.8, CH_2Cl_2); δ_H (200 MHz; 340 K; $CDCl_3$) 7.36–7.12 (5H, m, Ph), 6.49 (1H, d, *J* 15.9 Hz, C_8-H), 6.26 (1H, dt, *J* 15.9, 6.8 Hz, C_7-H), 4.71 (1H, d, *J* 2.1 Hz, C_2-H), 4.47 (1H, dd, *J* 5.2, 2.1 Hz, C_3-H), 4.19–4.10 (1H, m, C_5-H), 4.01 (1H, dd, *J* 7.9, 5.2 Hz, C_4-H), 3.73 (3H, s, C_1–OCH_3), 2.65–2.39 (2H, m, C_6-H), 1.61 (3H, s, $NC(CH_3)_A(CH_3)_BO$), 1.56 (3H, s, $NC(CH_3)_A(CH_3)_BO$), 1.49 (9H, s, $OC(CH_3)_3$), 1.41 (6H, s, $OC(CH_3)_2O$); δ_C (50 MHz; 340 K; $CDCl_3$) 172.1, 151.9, 137.7, 133.0, 128.5, 127.1, 126.3, 125.6, 109.0, 96.8, 80.9, 80.1, 78.4, 75.2, 61.4, 52.2, 36.6, 28.5, 27.7, 27.4, 27.2 (2C). A second fraction gave pure (7*Z*)-alkene (7*Z*)-**2** (t_R ≈28.5 min) as a viscous, clear, colourless liquid (0.0080 g, 6.5%); $[\alpha]_D^{21}$ +3.7 (*c* 0.8, CH_2Cl_2); δ_H (200 MHz; 340 K; $CDCl_3$) 7.30–7.16 (5H, m, Ph), 6.58–6.52 (1H, m, C_8-H), 5.79 (1H, dt, *J* 11.7, 7.0 Hz, C_7-H), 4.68 (1H, d, *J* 2.1 Hz, C_2-H), 4.44 (1H, m, C_3-H), 4.22–4.10 (1H, m, C_5-H), 3.97 (1H, dd, *J* 7.8, 5.5 Hz, C_4-H), 3.73 (3H, s, C_1–OCH_3), 2.66–2.59 (2H, m, C_6-H), 1.58 (3H, s, $NC(CH_3)_A(CH_3)_BO$), 1.48 (3H, s, $NC(CH_3)_A(CH_3)_BO$), 1.42 (12H, s, $OC(CH_3)_3$, $OC(CH_3)_2O$), 1.40 (3H, s, $OC(CH_3)_2O$); δ_C (50 MHz; 340 K; $CDCl_3$) 172.1, 151.8, 137.5, 131.4, 128.9, 128.2, 127.2, 126.8, 109.1, 96.8, 80.9, 80.4, 78.3, 75.3, 61.5, 52.2, 32.5, 28.4, 27.6, 27.4, 27.2, 27.0.

(4*R*,5*S*)-3-*tert*-Butyl-5-methyl-4-{(4*S*,5*S*)-5-[(2*E*,4*E*)-5-(4-ethoxyphenyl)penta-2,4-dienyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2,2-dimethyloxazolidine-3,5-dicarboxylate (7*E*,9*E*)-3 and (4*R*,5*S*)-3-*tert*-butyl-5-methyl-4-{(4*S*,5*S*)-5-[(2*Z*,4*E*)-5-(4-ethoxyphenyl)penta-2,4-dienyl]-2,2-dimethyl-1,3-dioxolan-4-yl}-2,2-dimethyloxazolidine-3,5-dicarboxylate (7*Z*,9*E*)-3

To a suspension of phosphonium salt **27** (0.083 g, 0.16 mmol) in benzene (4.0 mL) at 0 °C was added drop-wise a solution of potassium bis(trimethylsilyl)amide (0.50 M in toluene, 0.32 mL, 0.16 mmol). The crimson solution was allowed to warm to room temperature for 10 min and was cooled to 0 °C. A solution of a crude mixture of aldehyde (4*S*,5*S*)-**4** and aldehyde (4*R*,5*R*)-**4** [(4*S*,5*S*)-**4** : (4*R*,5*R*)-**4** = 7 : 1, 0.065 g, 0.16 mmol] in benzene (2.0 mL) was added. The brown solution was allowed to warm to room temperature and was stirred for 25 min. Dry methanol (3.0 mL) was added followed by ammonium chloride solution (sat. aq., 10 mL) and the crude product was extracted into ethyl acetate (3 × 30 mL). The combined organic layers were dried (Na_2SO_4), filtered and concentrated under reduced pressure to give an orange residue (0.14 g). Flash chromatographic purification (15% ethyl acetate : hexanes) of the crude product gave an inseparable mixture of dienes **3** as a viscous, clear colourless liquid (0.056 g, 63%); R_f 0.30 (20% ethyl acetate : hexanes), 0.11 (10% ethyl

acetate : hexanes); $[\alpha]_D^{17}$ +4.7 (*c* 1.4, CH_2Cl_2); ν_{max} (thin film)/cm^{-1} 1763 (m), 1740 (m), 1701 (s, C=O), 1605, 1510 (s, Ar(C=C)), 1250, 1175, 1089 (C–O–C); HRMS (+ESI) calc. for $C_{30}H_{43}O_8N$ + Na 568.2886, found 568.2871; *m*/*z* (+ESI) 584 ([M + K]$^+$, 28%), 568 ([M + Na]$^+$, 100), 512 (43). Preparative HPLC purification (RTI Zorbax Sil, 10% ethyl acetate : hexanes) of a portion of the purified product (0.029 g) gave pure (7*E*,9*E*)-diene (7*E*,9*E*)-**3** (t_R ≈33.0 min) as a viscous, clear, colourless liquid (0.020 g, 23%); $[\alpha]_D^{18}$ −1.8 (*c* 1.8, CH_2Cl_2); δ_H(200 MHz; 340 K; $CDCl_3$) 7.29–7.21 (2H, m, Ar-H), 6.85–6.78 (2H, m, Ar-H), 6.61 (1H, dd, *J* 15.5, 10.0 Hz, C_9-H), 6.39 (1H, d, *J* 15.6 Hz, C_{10}-H), 6.26 (1H, dd, *J* 15.1, 10.0 Hz, C_8-H), 5.79 (1H, dt, *J* 14.8, 7.3 Hz, C_7-H), 4.70 (1H, d, *J* 2.1 Hz, C_2-H), 4.45 (1H, dd, *J* 5.1, 2.0 Hz, C_3-H), 4.11–3.94 (4H, m, C_5-H, C_4-H, OCH_2CH_3), 3.76 (3H, s, C_1–OCH_3), 2.52–2.31 (2H, m, C_6-H), 1.61 (3H, s, $NC(CH_3)_A(CH_3)_BO$), 1.57 (3H, s, $NC(CH_3)_A(CH_3)_BO$), 1.50 (9H, s, $OC(CH_3)_3$), 1.42–1.35 (9H, m, $OC(CH_3)_2O$, OCH_2CH_3); δ_C (50 MHz; 340 K; $CDCl_3$) 172.1, 158.7, 151.9, 133.7, 130.9, 130.5, 128.4, 127.5, 127.1, 115.0, 109.0, 96.8, 80.9, 80.1, 78.4, 75.3, 63.7, 61.4, 52.2, 36.5, 28.5, 27.7, 27.4, 27.2, 27.1, 14.8. A second fraction gave pure (7*Z*,9*E*)-diene (7*Z*,9*E*)-**3** (t_R ≈29.0 min) as a viscous, clear, colourless liquid (0.0067 g, 7.5%); $[\alpha]_D^{18}$ +10.3 (*c* 0.57, CH_2Cl_2); δ_H (200 MHz; 340 K; $CDCl_3$) 7.36–7.32 (2H, m, Ar-H), 6.97–6.81 (3H, m, C_9-H, Ar-H), 6.49 (1H, d, *J* 15.9 Hz, C_{10}-H), 6.26 (1H, t, *J* 11.0 Hz, C_8-H), 5.56 (1H, dt, *J* 10.9, 7.5 Hz, C_7-H), 4.72 (1H, d, *J* 2.2 Hz, C_2-H), 4.49 (1H, dd, *J* 4.6, 1.9 Hz, C_3-H), 4.15–4.00 (4H, m, C_5-H, C_4-H, OCH_2CH_3), 3.75 (3H, s, C_1–OCH_3), 2.61 (2H, t, *J* 6.2 Hz, C_6-H), 1.63 (3H, s, $NC(CH_3)_A(CH_3)_BO$), 1.58 (3H, s, $NC(CH_3)_A(CH_3)_BO$), 1.50 (9H, s, $OC(CH_3)_3$), 1.44–1.37 (9H, m, $OC(CH_3)_2O$, OCH_2CH_3); δ_C (50 MHz; 340 K; $CDCl_3$) 172.2, 158.1, 151.9, 132.9, 131.5, 130.5, 127.8, 125.6, 122.5, 115.0, 109.1, 96.9, 80.9, 80.3, 78.4, 75.2, 63.7, 61.5, 52.3, 31.8, 28.5, 27.8, 27.5, 27.2 (2C), 14.8.

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