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Rapid Assembly of the Polyhydroxylated β-Amino Acid Constituents of Microsclerodermins C, D, and E

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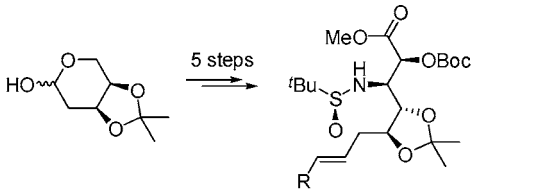
ABSTRACT



APTO constituent of Microsclerodermin C and D: R = Ph
AETD constituent of Microsclerodermin E: R = (*E*)-CH=CH(*p*-C_6H_4OEt)

A very short and efficient synthesis of protected derivatives of APTO and AETD, the complex polyhydroxylated β-amino acid residues present in microsclerodermins C, D, and E, is described. The targets are obtained in only five steps, in 23% and 16% overall yields, respectively. The key transformation involves the completely diastereoselective two-carbon homologation of appropriately selected intermediate chiral sulfinimines.

The microsclerodermins A−I and two dehydro derivatives constitute a family of complex cyclic peptides isolated from the lithistid sponges *Microscleroderma* sp. and *Theonella* sp. which possess antifungal and antitumor activities.[1] The family is characterized by a 23-atom macrocyclic ring comprising six amino acid residues, three of which are common. The more complex residues, which vary within the family, are a modified tryptophan, an unusual 3-aminopyrrolidone-4-acetic acid moiety, and a polyhydroxylated β-amino acid residue containing four or five contiguous chiral centers. In microsclerodermins C and D (Figure 1) as well as their dehydro counterparts which contain a dehydropyrrolidone moiety, the latter constituent is (2*S*,3*R*,4*S*,5*S*,7*E*)-3-amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid (APTO). In microsclerodermin E (Figure 1) this component is (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) (Figure 1).

To date, only the total synthesis of microsclerodermin E has been reported,[2] in which the AETD fragment was obtained in 16 steps and 10% overall yield. Recently, 12-step synthetic pathways to APTO (12% overall) and AETD (9% overall) derivatives were disclosed.[3] In related studies,

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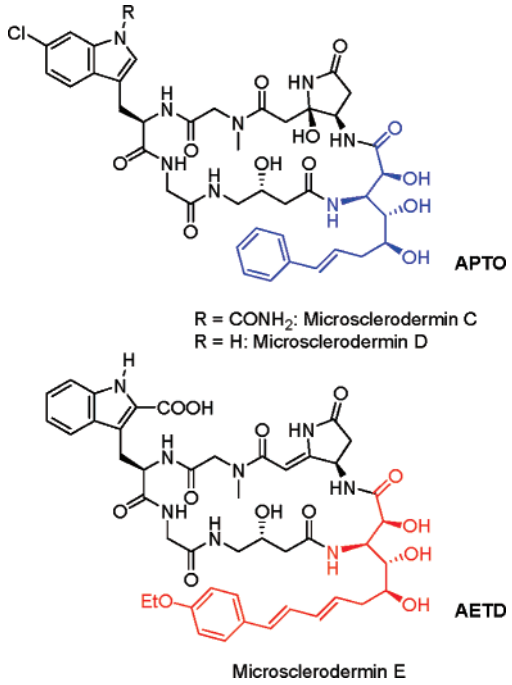
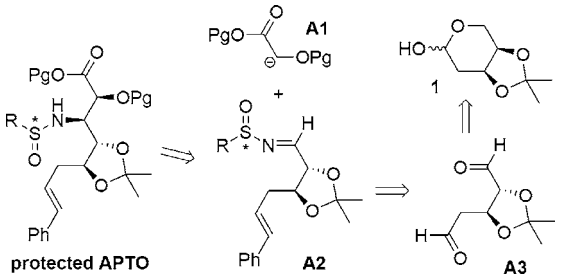


Figure 1. Microsclerodermins C, D, and E, with the APTO and AETD fragments highlighted in blue and red, respectively.

some synthetic approaches to building blocks for the construction of microsclerodermins A and B have appeared.[4]

Herein, we present our synthetic efforts in this field, providing a rapid and efficient construction of protected APTO and AETD derivatives. The retrosynthetic analysis for protected APTO, the first target, is outlined in Scheme 1. We envisaged construction of the α-hydroxy-*β*-amino acid

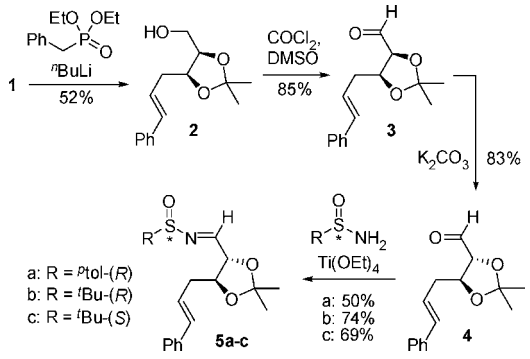
Scheme 1. Retrosynthetic Analysis for Protected APTO



structural feature by stereocontrolled two-carbon homologation of chiral sulfinimine **A2** with anion **A1**.[5] Sulfinimine **A2** should be accessible via a differentiated dialdehyde synthon **A3**, for which a convenient precursor should be the readily available 2-deoxy-D-ribose acetonide **1**.[6]

Initial studies of the Wittig reaction of acetonide **1** with $PhCH{=}PPh_3$ provided the olefin **2** as an inseparable mixture of *E*/*Z*-isomers. Complete *E*-selectivity was achieved using Horner−Wadsworth−Emmons methodology (Scheme 2).

Scheme 2. Synthesis of Chiral Sulfinimines **5a**−**c**



Best results (see Supporting Information) were obtained using ^{n}BuLi as base, which afforded pure **2** in 52% yield. A modified Swern oxidation[7] of hydroxy acetonide **2** provided aldehyde **3** in 85% yield. Ensuing epimerization of the α-stereocenter with K_2CO_3 in methanol using an adaptation of the literature method[8] gave aldehyde **4** with the requisite stereochemistry in 83% yield. Aldehyde **4** was then converted into chiral sulfinimines **5a** (50%), **5b** (74%), and **5c** (69%) by reaction with (*R*)-(−)-*p*-toluenesulfinamide, (*R*)-(+)-*tert*-butanesulfinamide, and (*S*)-(−)-*tert*-butanesulfinamide, respectively, in the presence of $Ti(OEt)_4$.[9]

In support of the planned two-carbon homologation, we were encouraged by a recent report that the addition of enolates of α-hydroxyacetates bearing a bulky *O*-protecting group (Boc) to simple chiral sulfinimines proceeded in a highly diastereoselective manner.[10] This observation was exploited in an illustrative synthesis of the taxol side chain with a 2*R*,3*S* configuration. Thus, we examined this reported procedure with a view to obtaining protected APTO fragments **7** with a 2*S*,3*R* configuration by reaction of sulfinimines **5** with protected α-hydroxyacetates **6** (Table 1). Initially, the products were obtained in disappointingly low yields, but inversing the reagent addition order (addition of sulfinimine to the enolate) provided a dramatic improvement. ^{t}Bu-sulfinimines **5b** and **5c** (entries 3, 4, 6) provided much higher selectivities and better yields than *p*-tolylsulfinimine

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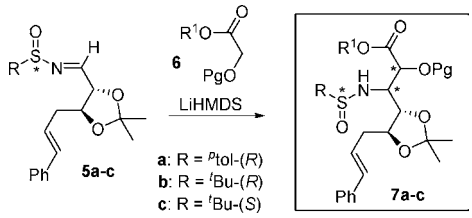
Table 1. Synthesis of Protected APTO **7**



entry	5/7	**6** (R^1/Pg)	yield (%)	dr[a]	config.[e]
1	**a**	Boc/Boc	56	*b*	–
2	**a**	All/Boc	57	*b*	–
3	**b**	All/Boc	72	78:22:0:0	–
4	**b**	Me/Boc	66	>99:0:0:0[c]	2*R*,3*S*
5	**b**	Me/Tr	*d*	–	–
6	**c**	Me/Boc	94	>99:0:0:0[c]	2*S*,3*R*

[a] As judged by NMR. [b] Complex mixtures obtained. [c] Only one isomer observed. [d] Reagent decomposed. [e] Determined by X-ray crystallography. All = allyl; Tr = trityl.

5a (entries 1, 2). The system appeared very sensitive to substituent effects: changing the enolate from **6** (All/Boc) to **6** (Me/Boc) improved the stereoselectivity to effective completeness, whereas the enolate from **6** (Me/Tr) decomposed in the same conditions (entries 3−5). The reactions of **6** (Me/Boc) with **5b** and **5c** thus satisfyingly provided pure APTO fragments **7b** and **7c** (R = tBu, R^1 = Me, Pg = Boc) as single diastereomers in 66% and 94% yield, respectively (entries 4, 6).

The absolute stereochemistry of **7b** and **7c** was determined by means of single-crystal X-ray diffraction (Figure 2). To our surprise we found that **7b** (derived from (*R*)-(+)-*tert*-butanesulfinamide) possessed the 2*R*,3*S* configuration, whereas **7c** (derived from (*S*)-(−)-*tert*-butanesulfinamide) possessed the desired 2*S*,3*R* configuration![11]

The formation of **7c** from **5c** cannot be explained rationally by a 6/4 bicyclic transition-state model. A more comfortable explanation for the observed stereoselectivity might be a nonchelated reaction pathway (Figure 3a), proposed earlier for similar systems.[12] Alternatively, a 6/6 chelated bicyclic chairlike transition state where the most bulky groups are in equatorial positions can be proposed (Figure 3b). Both these models are in accordance with the observed steric demands of our system: the sulfinimine moiety and the *O*-protecting group of **6** need to be as bulky as possible, while only the diminutive methyl ester of **6** gives complete selectivity.

It is noteworthy that the stereochemical outcome of this two-carbon homologation is controlled by the sulfinyl group only and thus proceeds independently of other neighboring chiral centers in the molecule. This chiral predominance phenomenon was previously noted for sulfinimine one-carbon homologation with cyanide.[9]

(11) These stereochemical observations are in contradiction with the chemical structures presented in ref 10 and, in consequence, are in disaccord with arguments presented therein to account for the stereoselectivity.

(12) Fujisawa, T.; Kooriyama, Y.; Shimizu, M. *Tetrahedron Lett.* **1996**, *37*, 3881.

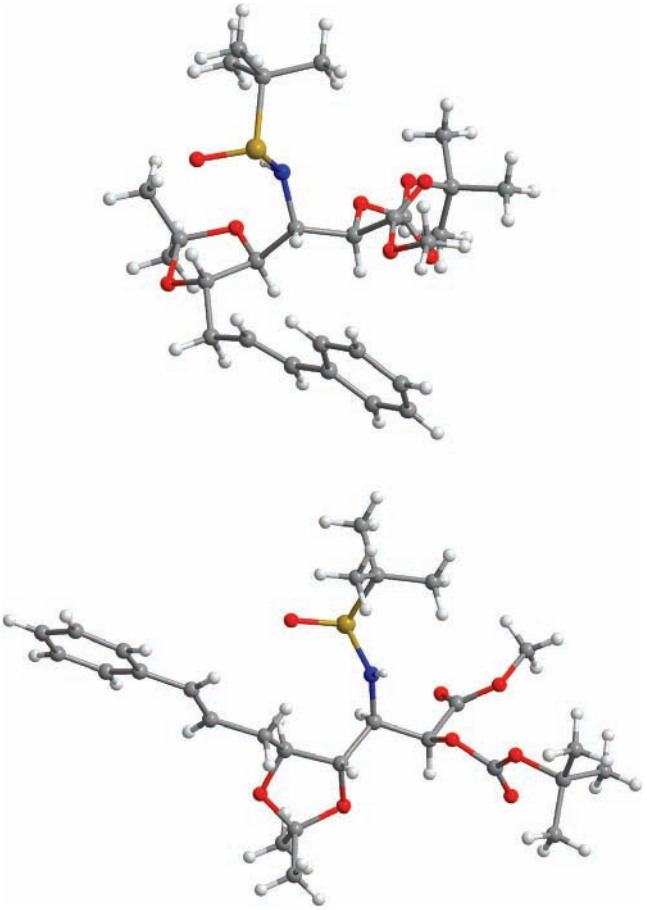


Figure 2. X-ray structures of **7b** (top) and **7c** (bottom).

Having developed this short stereoselective pathway to the protected APTO fragment of microsclerodermins C and D, we then turned our attention to the synthesis of the AETD fragment of microsclerodermin E (Scheme 3). In contrast to the results obtained in the synthesis of olefin **2**, all attempts to use Horner−Wadsworth−Emmons methodology proved fruitless for the synthesis of olefin **9** from **1**. After numerous explorations (see Supporting Information), access to the desired alcohol was only found possible through use of phosphonium bromide **8** in benzene solution in the presence of KHMDS as base.[3] The product was obtained as an *E*/*Z*-

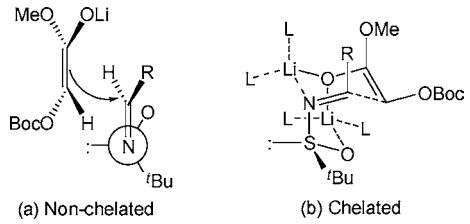
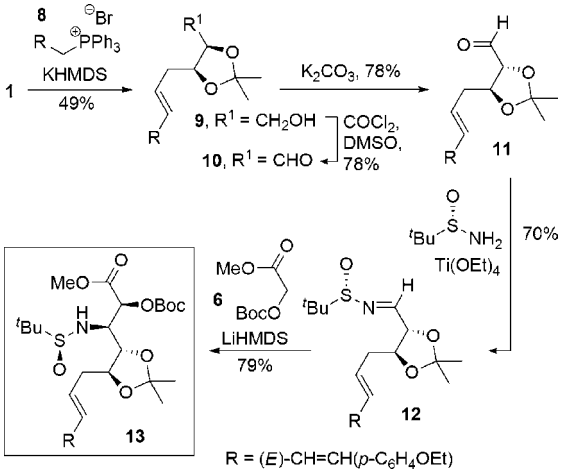


Figure 3. Two plausible models, (a) nonchelated and (b) chelated, for interactions of enolate **6** (Me/Boc) with **5c** leading to the observed selectivity of **7c**.

Scheme 3. Synthesis of Protected AETD **13**



mixture which was easily separated by column chromatography to furnish the desired pure (*E*)-**9** in 49% yield as well as 19% of pure (*Z*)-**9**. Swern oxidation of (*E*)-**9** (78%) followed by isomerization with K_2CO_3 (78%) provided aldehyde **11**. The latter was converted into sulfinimine **12** using (*S*)-(−)-*tert*-butanesulfinamide in 70% yield. Reaction with methyl *O*-Boc-hydroxyacetate **6** (Me/Boc) according to our optimized conditions then provided the protected AETD fragment **13** in 79% yield as a single diastereomer. Compound **13** showed spectral data which were very similar to those of **7c**.

In conclusion, we have established very short and effective syntheses of protected APTO **7c** and protected AETD **13**. These proceed in 23% and 16% overall yield, respectively, in only 5 steps from the readily available acetonide-protected 2-deoxy-D-ribose **1**. This approach compares favorably with the existing pathways for the preparation of comparable intermediates for the synthesis of microsclerodermins C, D, and E and is furthermore not restricted to small-scale synthesis.

Acknowledgment. We thank the French Ministry for Research for financial support.

Supporting Information Available: Full experimental procedures, characterization data, and NMR spectra for all intermediates and final products; optimization data for the synthesis of alcohols **2** and **9**; CIF files for **7b** and **7c**. This material is available free of charge via the Internet at http://pubs.acs.org.

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