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The Efficient Stereoselective Synthesis of (2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-Amino-6-methyl-12-(4-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic Acid (AMMTD), a Component of Microsclerodermins of Marine Sponge Origin, as Its Protected Form

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Abstract: The title acid, a component of microsclerodermins of marine sponge origin having five consecutive stereogenic centers, was efficiently synthesized as its protected form **1** from the alcohol **5** utilizing the stereoselective addition of anisole to the acetylenic triple bond and the anti-aldol reaction as key steps.
Keywords: Marine metabolites, Amino acid and derivatives, Aldol reactions, Addition reactions

Microsclerodermins A and B were isolated from the lithistid marine sponge *Microscleroderma* sp. collected near New Caledonia by Faulkner and co-workers.[1] They exhibit antifungal activities especially against *Candida albicans*, and proved to be 23-membered cyclic hexapeptides containing four unusual amino acid components, as shown in Fig. 1. The structure of AMMTD, (2*S*,3*R*,4*S*,5*S*,6*S*,11*E*)-3-amino-6-methyl-12-(4-methoxyphenyl)-2,4,5-trihydroxydodec-11-enoic acid, is quite unique and features five consecutive stereogenic centers. As a continuation of our studies on the synthesis of biologically active aquatic natural products,[2] we have attempted the total synthesis of this unique cyclic peptides.[3] We have already reported the stereoselective synthesis of the core building block **1'** for AMMTD.[4] We herein wish to report the efficient stereoselective synthesis of the AMMTD derivative **1** using a methodology different from the former one.

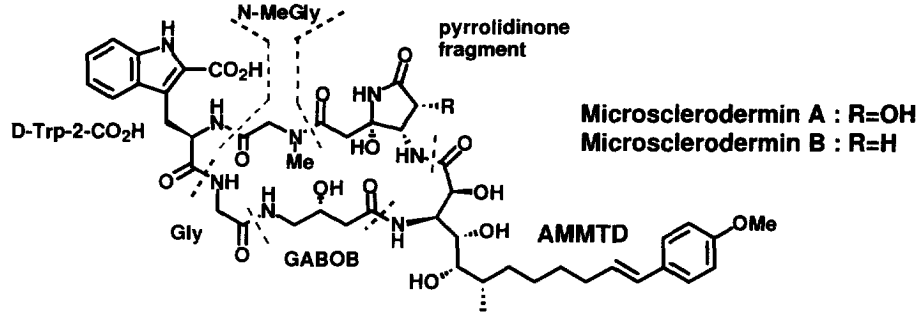

Fig. 1

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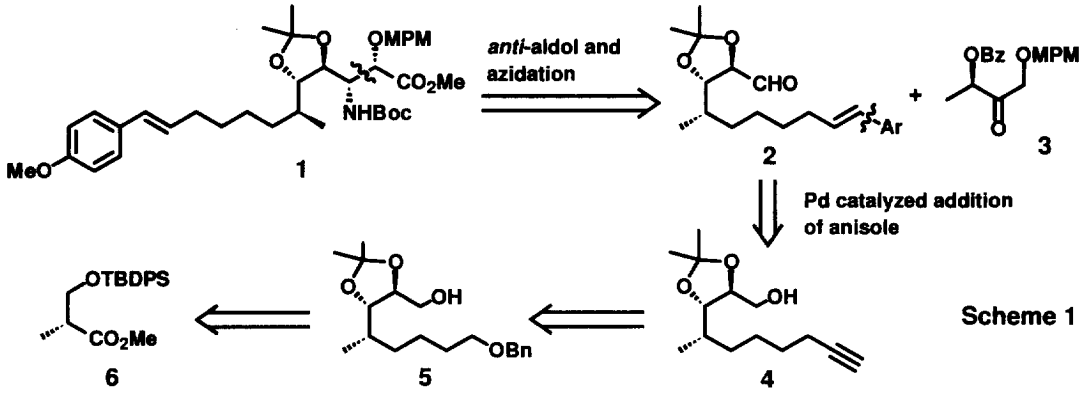
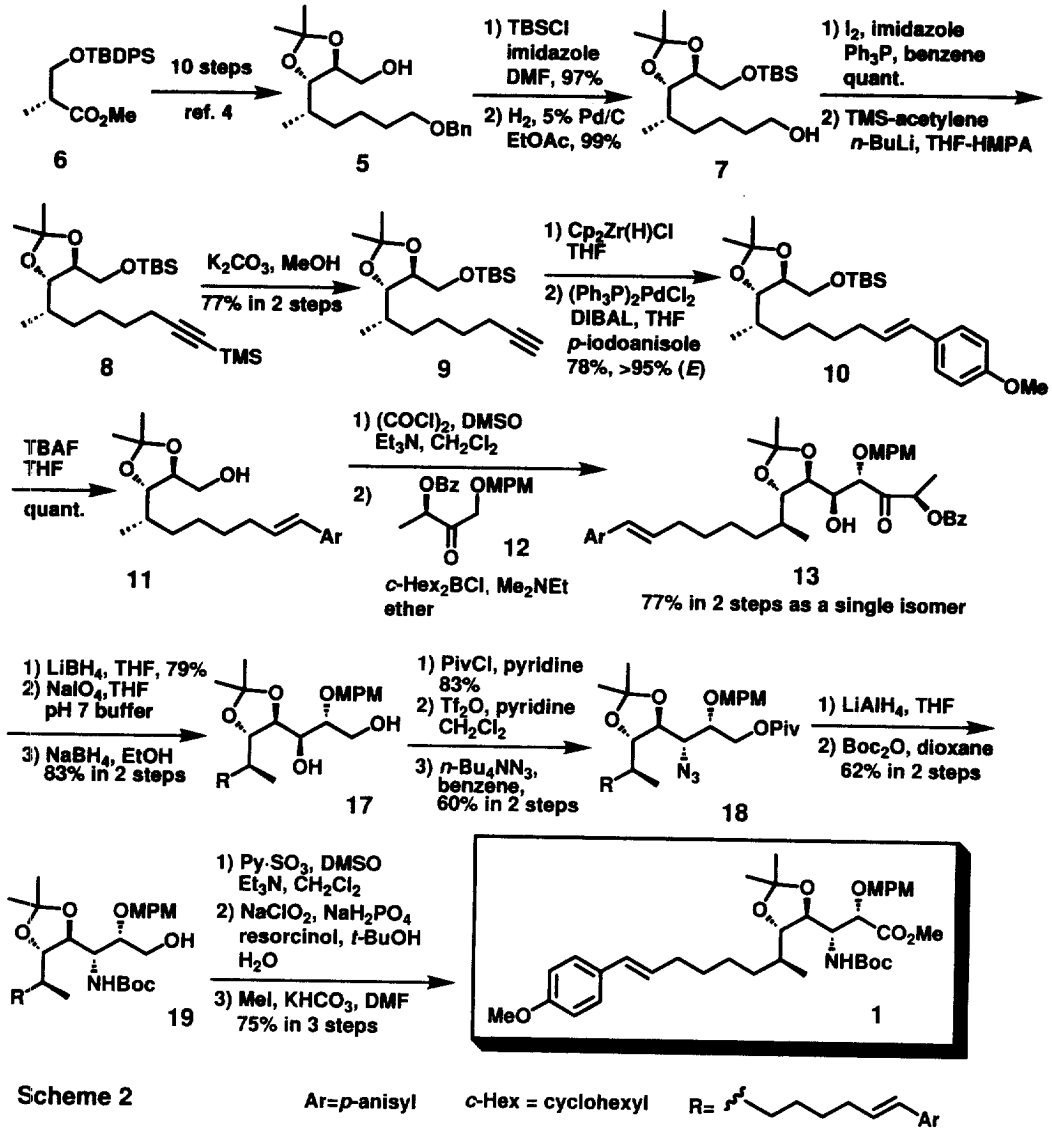
Our retrosynthetic analysis is illustrated in Scheme 1. The protected derivative **1** of AMMTD, the target of this synthesis, would be constructed by the anti-aldol reaction of the aldehyde **2** with the ketone **3** and then azidation as the key steps. The aldehyde **2** would be derived from the alkyne **4** through the palladium catalyzed addition reaction of anisole. The obvious starting material for the synthesis of **4** would be the acetonide alcohol **5**, previously prepared from the ester **6** in 10 steps.[4]



Boc : *t*-butoxycarbonyl MPM : *p*-methoxybenzyl Bz : benzoyl Bn : benzyl TBDPS : *t*-butyldiphenylsilyl

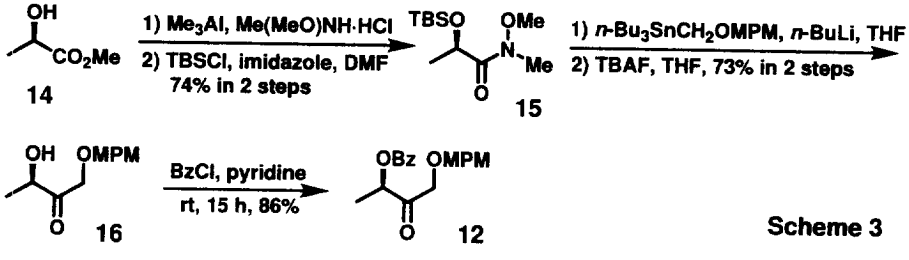
The acetonide alcohol **5** was first silylated with *tert*-butyldimethylsilyl chloride (TBSCl) and then catalytically hydrogenated over palladium-carbon to yield the alcohol **7**. Conversion of the alcohol **7** to the corresponding iodide was accomplished with iodine-imidazole-triphenylphosphine. The iodide produced was treated with lithium trimethylsilyl(TMS) acetylide to give the TMS-alkyne **8**, from which the TMS group was removed with potassium carbonate in methanol to furnish the alkyne **9**. Hydrozirconation of **9** followed by the addition of *p*-iodoanisole using bis(triphenylphosphine)palladium chloride-diisobutylaluminum hydride (DIBAL) according to Negishi's protocol[5] afforded the anisyl-(*E*)-alkene **10** in 78% yield. Removal of the TBS group from **10** with tetra-*n*-butylammonium fluoride (TBAF) yielded the alcohol **11**, which was oxidized under the Swern conditions. The resulting aldehyde underwent the anti-aldol reaction with the ketone **12** to give the keto alcohol **13** as a single isomer using dicyclohexylboron chloride in the presence of dimethylethylamine.[6] The ketone **12** was prepared from methyl (*R*)-lactate **14**, which was converted to the TBS Weinreb amide **15** by treatment with N-methoxy-N-methylaminoaluminum and then TBSCl-imidazole. The reaction of the Weinreb amide **15** with *p*-methoxybenzyl(MPM) oxymethyl tributyl stannane-butyllithium followed by TBAF afforded the keto alcohol **16**, whose hydroxyl group was protected with benzoyl chloride to give the ketone **12**, as shown in Scheme 3.

The keto alcohol **13** was reduced with lithium borohydride to give the triol. The *vic*-diol part of the triol was cleaved with sodium periodate, followed by reduction of the resulting aldehyde with sodium borohydride to give the desired alcohol **17** in 83% yielded in two steps. After protection of the primary alcohol with pivaloyl chloride (PivCl), conversion of the secondary alcohol to the azide was achieved in 60% yield by sequential treatment with triflic anhydride (Tf_2O) and then tetra-*n*-butylammonium azide. Reduction of the obtained azide **18** with lithium aluminum hydride followed by the Boc (*tert*-butoxycarbonyl) protection afforded the N-Boc alcohol **19** in 62% yield (2 steps). The final step for the synthesis of the AMMTD derivative **1** was the conversion of the primary hydroxyl function to the ester one, which was achieved in three steps : (1) the



Scheme 2

Ar=*p*-anisyl *c*-Hex = cyclohexyl R=



Scheme 3

Parikh-Doering oxidation, (2) the oxidation with sodium chlorite, and (3) the methyl esterification to give the desired AMMTD derivative **1**.

Thus, we have accomplished the synthesis of the AMMTD derivative **1**, a requisite building block for the total synthesis of microsclerodermins, by the stereoselective construction of five consecutive stereogenic centers. We are now actively conducting the synthetic studies of microsclerodermins.

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References and Notes

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2. For our recent work in this area, see Yokokawa, F. ; Shioiri, T. *J. Org. Chem.* **1998**, *63*, 8638-8639.
3. A part of this work was presented at the First International Peptide Symposium held in Kyoto, Japan, on November 30-December 5, 1997 and at the 35th Japanese Peptide Symposium held in Saga, Japan, on October 7-9, 1998.
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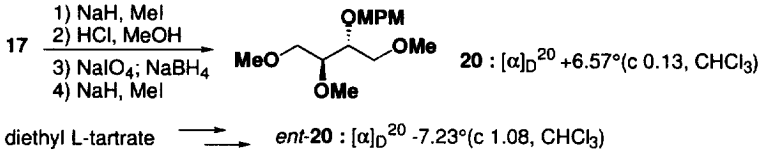
6. Paterson, I. ; Wallace, D. J. ; Velazquez, S. M. *Tetrahedron Lett.* **1994**, *35*, 9083-9086 and 9087-9090, and references cited therein. The absolute configurations at the newly formed stereogenic centers were confirmed as follows: **17** was converted to **20**; analogously, *ent*-**20** was obtained from diethyl L-tartrate. ^{1}H-NMR and $[\alpha]_D$ of **20** and *ent*-**20** unambiguously revealed the absolute configurations.



7. **1**, a colorless oil: $[\alpha]_D^{27}$ -8.29°(c 0.82, $CHCl_3$); IR ν_{max}^{neat} cm^{-1} 3445, 1755, 1743, 1615, 1504, 1456, 1304, 1211; ^{1}H-NMR ($CDCl_3$) δ 0.87 (3H, d, *J* = 6.6Hz, **CH3**CH) 1.11-1.57 (7H, m, **CH(CH2)3**) 1.37 (9H, s, **Me3**C) 1.41 (3H, s, **Me2**C) 1.43 (3H, s, **Me2**C) 2.16-2.18 (2H, m, **CH2**CH=CH) 3.72 (3H, s, CO_2**Me**) 3.78 (3H, s, **OMe**) 3.79 (3H, s, **OMe**) 3.72-3.84 (1H, m, CH_3CH**CH**) 3.84-3.93 (1H, m, **CH**OMPM) 4.12-4.19 (1H, m, CH_3CHCH**CH**) 4.41 (2H, s, O**CH2**Ar) 4.70 (1H, d, *J* = 10.9Hz, **CH**NHBoc) 4.88 (1H, d, *J* = 10.2Hz, **NH**) 6.06 (1H, dt, *J* = 6.6, 15.8Hz, **CH**=CHAr) 6.34 (1H, d, *J* = 15.8Hz, CH=**CH**Ar) 6.81-6.89 (4H, m, MeO**Ar (o)**) 7.19-7.32 (4H, m, MeO**Ar (m)**); ^{13}C-NMR ($CDCl_3$) δ 16.58, 26.61, 27.72, 27.81, 28.17, 29.68, 30.89, 32.94, 36.12, 52.00, 55.25, 56.01, 72.81, 76.53, 77.09, 79.64, 84.54, 109.18, 113.72, 113.87, 126.95, 128.84, 129.11, 129.41, 129.93, 130.76, 155.27, 158.59, 159.47, 171.58; HRMS (EI) m/z calcd. for $C_{37}H_{53}NO_9$: 655.3737. Found: 655.3720; Anal. calcd for $C_{37}H_{53}NO_9$: C, 67.76; H, 8.15; N, 2.14. Found : C, 67.49; H, 8.07; N, 2.12.