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Synthetic Studies of Microsclerodermins. A Stereoselective Synthesis of a Core Building Block for (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)

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Abstract: A core building block **3** for (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 (**2**, AMMTD) has been efficiently synthesized using the Sharpless asymmetric dihydroxylation and the Dondoni's furan addition to a nitrone derivative as key steps. The 2-furyl group has been used as the carboxyl synthon.© 1997 Elsevier Science Ltd.

Microsclerodermins A (**1a**, R=H) and B (**1b**, R=OH) have been isolated from a deep sea sponge of the genus *Microscleroderma* sp.[1] These 23-membered cyclic hexapeptides have intriguing antifungal activities against *Botrytic cinerea*, *Candida albicans*, *Fusarium oxysporum*, *Helminthosporium sativum*, and *Pyricularia oryzae*. Especially, they inhibit the growth of *Candida albicans* at a loading of 2.5 μg/disk in the standard disk assay, but their other biological activities have not yet been clarified.

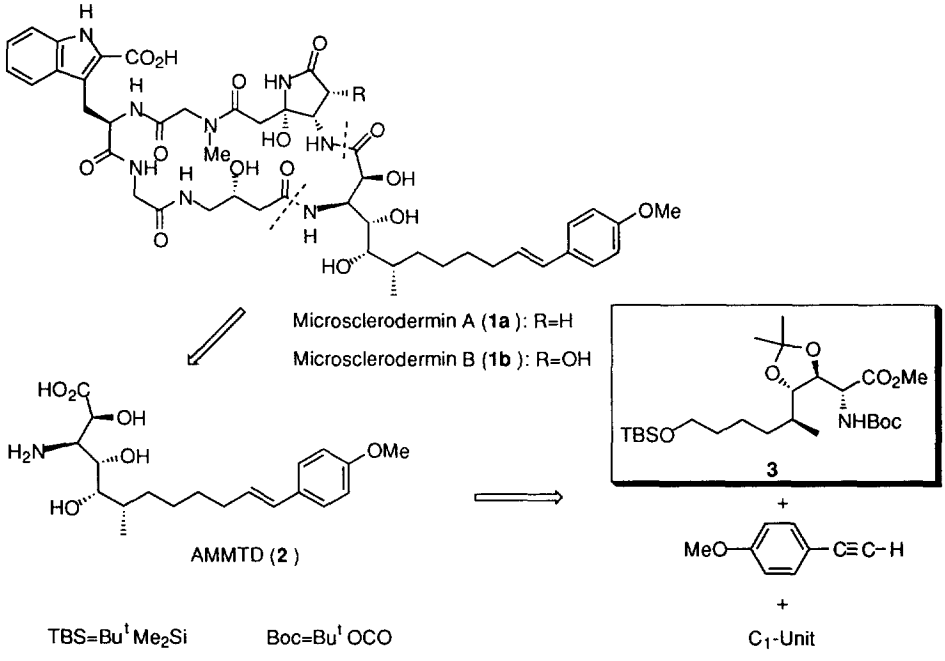
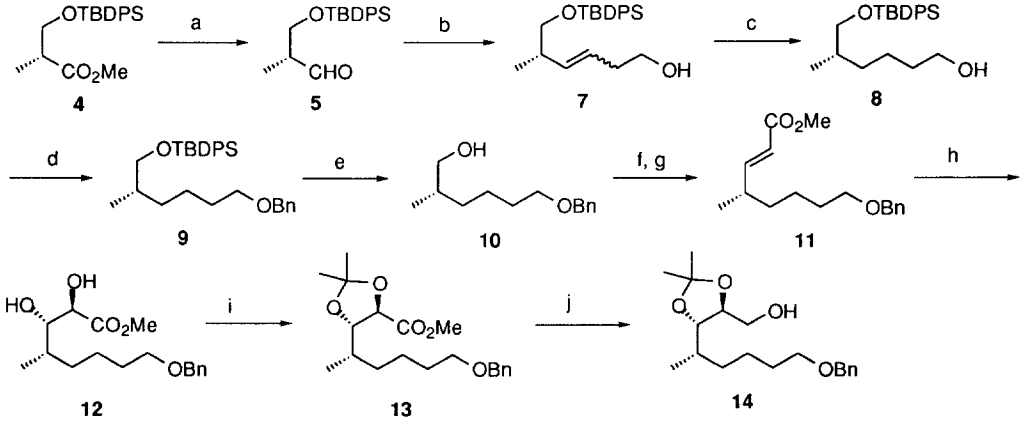


Fig. 1

Microsclerodermins contain four unusual amino acids, one of which (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 (**2**, AMMTD) features five consecutive stereogenic centers, as shown in Fig. 1. As a continuation of our studies on the synthesis of marine natural products,[2] we have begun the total synthesis of these unique cyclic peptides. This is the first approach toward the total synthesis of **1a** and **1b**. Herein, we report the stereoselective construction of a core building block **3** of AMMTD (**2**) using the Sharpless asymmetric dihydroxylation[3] and the Dondoni's furan addition to a nitrone derivative[4] as key steps. The 2-furyl group has been used as the carboxyl synthon.[5]

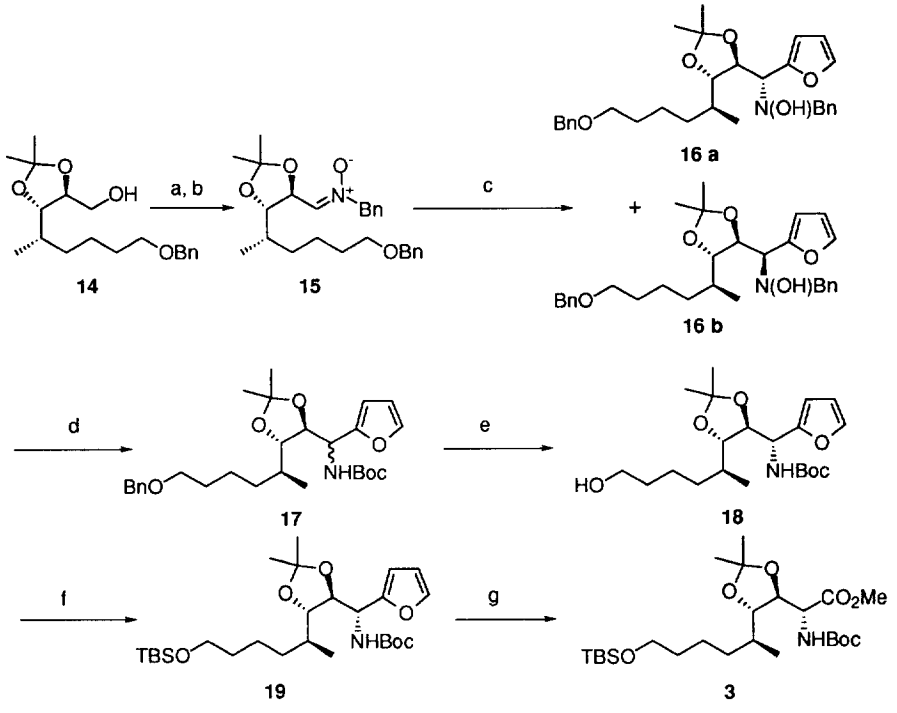
Our synthesis started from methyl (*R*)-3-O-*tert*-butyldiphenylsiloxy-2-methylpropionate (**4**).[6] Reduction of **4** with diisobutylaluminum hydride (DIBAL) gave the aldehyde **5**, which without purification underwent the Wittig reaction with the ylide derived from the phosphonium salt **6**[7] to give the alkene **7** as a mixture of (*E*)-and (*Z*)-isomers. Catalytic hydrogenation of **7**, produced by method A in Scheme 1, with palladium on carbon afforded the saturated alcohol **8**. Benzylation of the alcohol **8** with benzyl bromide in the presence of sodium hydride almost quantitatively produced the benzyl ether **9**, from which the desilylation with tetra-n-butylammonium fluoride (TBAF) gave the primary alcohol **10** in excellent yield. The alcohol **10** was converted to the corresponding MTPA ester to check its optical purity. The ^{1}H NMR spectral study of the MTPA ester revealed that 31% racemization had occurred. We thought that the racemization of the aldehyde **5** occurred at the stage of the Wittig reaction because of the strong basicity of the alkoxide produced from the ylide from **6**. Thus, we temporarily protected the hydroxyl group of **6** with chlorotrimethylsilane (TMSCl) to avoid the formation of the alkoxide before addition of the aldehyde **5** according to method B in Scheme 1. As we expected, no racemization occurred at the Wittig stage and we obtained the alcohol **10** as an optically pure form by the analogous conversion of **7** to **10**.

The Swern oxidation of the primary alcohol **10**, followed by the Wittig reaction with methoxycarbonylmethylenetriphenylphosphorane quantitatively afforded the (*E*)-α,β-unsaturated ester **11**. Asymmetric dihydroxylation[3] of **11** with AD-mix-α in the presence of methanesulfonamide gave the diol **12**, which was treated with 2,2-dimethoxypropane to give the ketal **13** with 96% diastereoisomeric excess in almost quantitative yield.[8,9] Reduction of **13** with lithium borohydride furnished the primary alcohol **14** in excellent yield (Scheme 1).



Scheme 1. a) DIBAL, CH_2Cl_2, -78℃, 30 min. b) (Method A) $[Ph_3P^+(CH_2)_3OH]Br^-$(**6**), *n*-BuLi (2 eq), THF, 0℃, 30 min; **5**, -78℃, 30 min, 68% (from **4**, *31% racemization*). (Method B) **6**, *n*-BuLi (2 eq), THF, 0℃, 30 min; TMSCl (1 eq), 0℃, 30 min; **5**, -78℃, 30 min; 1M $KHSO_4$, rt, 30 min, 63% (from **4**, *no racemization*). c) H_2, Pd/C, MeOH, rt, 12 h, 68%. d) NaH, DMF, THF, -15℃, 30 min; BnBr, rt, 6 h, 99%. e) TBAF, THF, rt, 2 h, 94%. f) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78℃, 30 min, 0℃, 1 h. g) $Ph_3P{=}CHCO_2Me$, CH_2Cl_2, rt, 12 h, 99% (in 2 steps). h) AD-mix-α, $MeSO_2NH_2$, *t*-BuOH, H_2O, 4℃, 15 h. i) 2,2-dimethoxypropane, CSA, rt, 12 h, 97 % (in 2 steps), 24:1 selectivity. j) $LiBH_4$, THF, rt, 12 h, 94%.

After the Swern oxidation of **14**, condensation of the resulting aldehyde with N-benzylhydroxylamine[10] afforded the nitrone derivative **15** in 93% yield. The addition of 2-furyllithium to the nitrone **15** in the presence of diethyl aluminum chloride[4] gave a mixture of the furyl adducts **16a** and **16b** in a ratio of 7:1. The one-pot N-debenzylation and N-dehydroxylation[4,10] of the mixture **16** with titanium trichloride in methanol and then treatment with silica gel furnished the primary amine, which was further protected with di-*tert*-butyl dicarbonate (Boc_2O) to give the Boc-amine **17** in 56% yield. The O-debenzylation from **17** was performed with sodium in liquid ammonia. Purification of the product on silica gel column afforded the debenzylated product **18** as a single isomer in 77% yield. Protection of the primary alcohol function was achieved with *tert*-butyldimethylchlorosilane (TBSCl) to give the TBS derivative **19**.[11] Ruthenium oxidation of the furyl group of **19**, followed by methyl esterification, afforded the desired methyl ester **3** as a colorless oil (Scheme 2).[12]



Scheme 2. a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, -78℃, 30 min, 0℃, 30 min. b) BnNHOH, $MgSO_4$, CH_2Cl_2, rt, 4 h, 93% (in 2 steps). c) 2-furyllithium, Et_2AlCl, THF, ether, -78℃, 1 h, 59%, 7:1 selectivity. d) $TiCl_3$, MeOH, H_2O, rt, 20 min; SiO_2, CH_2Cl_2, H_2O, rt, 15 h; Boc_2O, dioxane, rt, 15 h, 56%. e) Na, liq. NH_3, -33℃, 3 h; diastereomer separation by SiO_2 column chromatography, 77%. f) TBSCl, imidazole, DMF, rt, 13 h, 99%. g) RuO_2, $NaIO_4$, CCl_4, MeCN, H_2O, rt, 15 min; MeI, $KHCO_3$, DMF, rt, 12 h, 65% (in 2 steps).

In summary, we have achieved the efficient construction of the core building block **3** for AMMTD (**2**) containing 4 consecutive stereogenic centers from the readily available starting material **4**. The synthetic studies toward microsclerodermins as well as AMMTD are now actively being conducted in our laboratories.

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8. The dihydroxylation using osmium tetroxide in the presence of N-methylmorpholine-N-oxide sluggishly proceeded to give a mixture of **13** and its diastereoisomer in a ratio of 1:1 after ketalization.
9. The absolute configuration of **13** is due to the general rule in the Sharpless asymmetric dihydroxylation utilizing AD-mix-α.[3]
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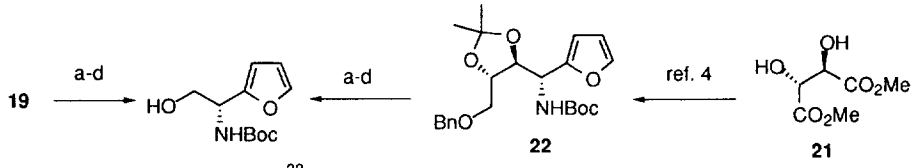
11. The absolute configuration at the newly formed stereogenic center containing the amino function was determined as follows: **19** was converted to **20**, as shown below, which was identified with the known[4] compound derived from dimethyl L-tartrate (**21**) via **22**.



20; $[\alpha]_D^{23}$=+44.4° (c=0.48, $CHCl_3$) from **19**

$[\alpha]_D^{23}$=+45.7° (c=0.74, $CHCl_3$) from **21**

a) HCl-MeOH. b) Boc_2O, dioxane, 58-60% in 2 steps. c) $NaIO_4$, THF, H_2O. d) $NaBH_4$, EtOH, 70-72% in 2 steps.

12. **3**, a colorless oil, $[\alpha]_D^{23}$-39.07° (c 0.87, $CHCl_3$); IR $\nu_{max}^{neat}{}_{cm}^{-1}$ 3445, 1744, 1718, 1499, 1367, 1256; ^{1}H-NMR (TMS/$CDCl_3$) δ 0.04 (6H, s, SiMe2), 0.88 (9H, s, SiCMe3), 0.95 (3H, d, *J*=6.9Hz CH_3CH), 1.30 (3H, s, CMe2), 1.35 (3H, s CMe2), 1.44 (9H, s, OCMe3), 1.11-1.67 (7H, m, CH_3CH (CH_2)3), 3.60 (2H, t, *J*=6.3Hz, CH_2OSi), 3.78 (3H, s, CO_2CH_3), 3.92-3.97 (2H, m, CHCHCHN), 4.48 (1H, brd, *J*=8.9Hz, CHN), 5.38 (1H, brd, *J*=8.9Hz, NH); *Anal.* Calcd for $C_{25}H_{49}NO_7Si$: C, 59.61; H, 9.80; N, 2.78. Found: C, 59.49; H, 9.56; N, 2.65.

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