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Stereoselective synthesis of the C1–C20 segment of the microsclerodermins A and B☆

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Abstract—An enantioselective route for the synthesis of key fragment C1–C20 resident in microsclerodermins A and B is described. The route features deoxygenative rearrangement of an hydroxy-alkynoate and a highly enantio- and diastereo-controled iterative dihydroxylation as key reactions, starting from *S*-(−)-citronellol.

The microsclerodermins (A–I) are a class of natural products, isolated from the lithistid sponge *Microscleroderma* sp., that display significant antifungal and *anti*-tumor activities.[1] Of the nine bioactive metabolites in this family, microsclerodermins A and B are two of the most biologically active with antifungal activity against *Candida albicans* (at 2.5 μg/disk). The microsclerodermins A and B have a complex molecular structure, comprising a 23-membered cyclic hexapeptide core, featuring four unusual amino acid residues, one of which is a very complex β-amino acid residue located in the C1–C20 region. This fragment has five contiguous asymmetric centers at C2–C6. Due to its biological profiles and the dense presence of stereogenic centers in the C1–C20 region, the target microsclerodermins A and B demand effective control of distal asymmetric induction, rendering the stereoselective preparation of this antifungal agent a challenging problem in chemical synthesis. To date only one research group has contributed to the partial synthesis of this complex natural product.[2]

In this letter, we describe an efficient synthesis of the C1–C20 subunit resident in microsclerodermins A and B. Our retrosynthetic analysis envisioned the late installment of the four contiguous stereocenters of **2** through the application of iterative Sharpless asymmetric dihydroxylation (SADH) on diene ester **3**. This, in turn could be obtained by triphenylphosphine-mediated rearrangement of alkynol **4** which was to be synthesized from commercially available *S*-(−)-citronellol **5** (Scheme 1).

As illustrated in Scheme 2, stereoselective synthesis of the C1–C20 segment of microsclerodermins A and B commenced with *S*-(−)-citronellol **5**, as a suitable chiral substrate.

The *S*-(−)-citronellol **5** was protected as its tetrahydropyranyl ether **6**. Compound **6** was subjected to ozonolysis to furnish aldehyde **7**, which was elaborated to unsaturated ester **8** by Wittig olefination. The stepwise reduction of the conjugate olefin (Mg–MeOH) followed by ester reduction to primary alcohol **9** was achieved using $LiAlH_4$.[3] The primary alcohol group in **9** was protected as a benzyl ether **10** by treatment with NaH and benzyl bromide in 90% yield. The selective release of one of the primary alcohols was achieved by using *p*-TSA in MeOH to realize **11**. This allowed us to extend the 'right-hand' side of the fragment. The oxidation of **11** using IBX[4] furnished aldehyde **12**, which was immediately exposed to lithiated ethylpropiolate to realize the formation of hydroxy alkynoate **4** as a diastereomeric mixture, which was not separated. The critical diene ester intermediate **3** was obtained from **4** by triphenylphosphine-mediated deoxygenative rearrangement via an allene.[5] This rearrangement allowed us to obtain the diene ester ready for the stereoselective incorporation of hydroxy groups via iterative Sharpless asymmetric dihydroxylation.

Keywords: Stereoselective; Deoxygenative rearrangement; Iterative Sharpless asymmetric dihydroxylation.
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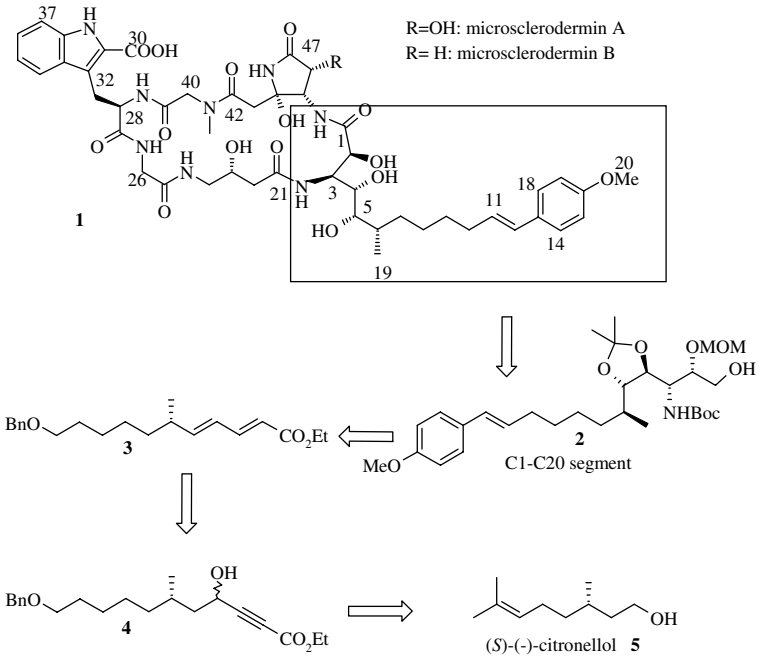
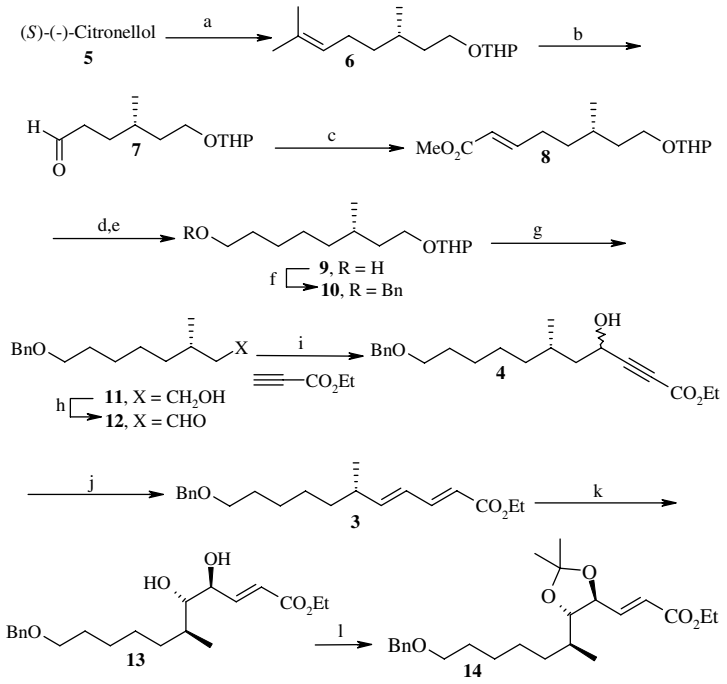


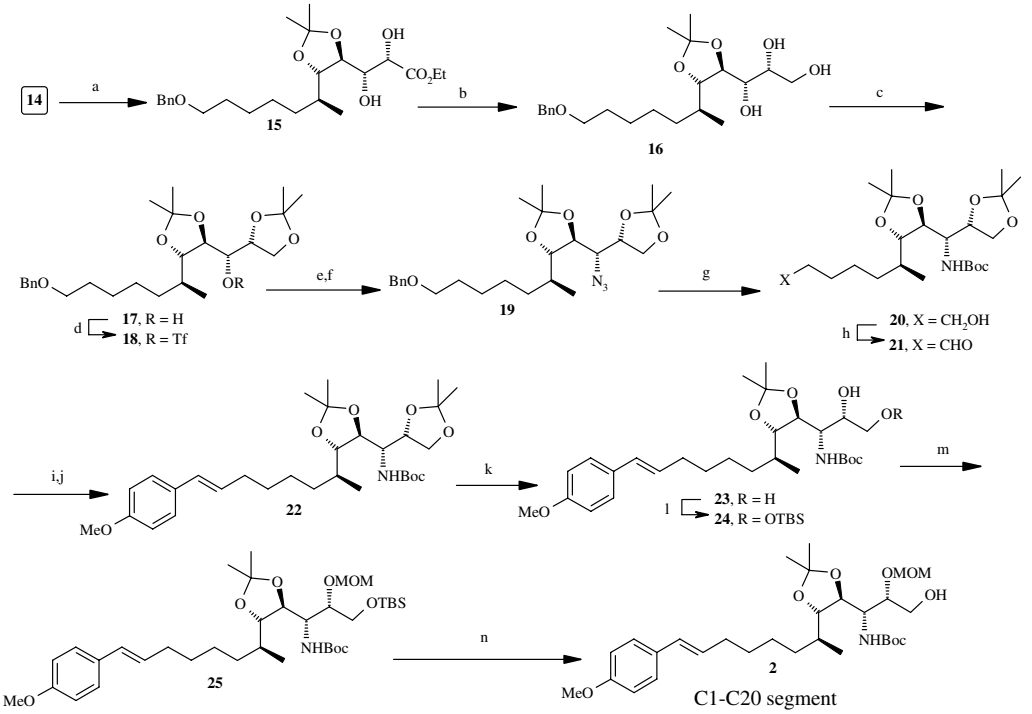
Scheme 1.



Scheme 2. Reagents, conditions and yields: (a) Dihydropyran, *p*-TSA (5 mol %), CH_2Cl_2, rt, 2 h, 98%; (b) O_3, DMS, CH_2Cl_2, −78 °C; (c) $Ph_3P{=}CHCOOMe$, benzene, rt, 84% (for two steps); (d) Mg/MeOH, rt, 12 h, 86%; (e) $LiAlH_4$, THF, 0 °C–rt, 96%; (f) BnBr, NaH, THF, 0 °C–rt, 90%; (g) *p*-TSA (5 mol %), MeOH, rt, 2 h, 93%; (h) IBX, DMSO-THF, rt, 3 h, 95%; (i) LiHMDS, THF, −78 °C, 2 h, 86%; (j) Ph_3P, benzene, rt, 90%; (k) AD mix-α$MeSO_2NH_2$, ^{t}BuOH–H_2O (1:1), 0 °C, 24 h; (l) 2,2 DMP, CSA (5 mol %), DCM, 1 h, 85%.

At first glance, Sharpless asymmetric dihydroxylation followed by a Sharpless asymmetric aminohydroxylation reaction seemed to be an option to establish the required four stereogenic centers at C2-3 and C4-5 in **2**. The enantio- and regio-selective Sharpless asymmetric dihydroxylation[6] of diene ester **3** with AD mix-α in ^{t}BuOH:H_2O (1:1) provided the diol **13** which was masked as its acetonide **14** using 2,2-dimethoxypropane and catalytic camphorsulfonic acid (CSA) in 85% yield (for two steps) with 96% de. The major isomer was separated by column chromatography (Scheme 3).

The regioselective incorporation of a *cis*-aminohydroxyl group was planned as the next step by Sharpless asymmetric aminohydroxylation,[7] however, this method was unsuccessful. Thus, we envisaged an asymmetric



Scheme 3. Reagents, conditions and yields: (a) AD-mix-β, ^{t}BuOH:H_2O, 0 °C, 87%; (b) $LiAlH_4$, THF, 1 h, 0 °C–rt, 80%; (c) 2,2-DMP, CSA (5 mol %), DCM, rt, 85%; (d) Tf_2O, pyridine, DCM, −10 °C; (e) Bu_4NBr, DCM, rt, 86% (for two steps); (f) NaN_3, DMF, 65 °C, 4 h, 82%; (g) $Pd(OH)_2/C$–H_2, $(Boc_2)O$, MeOH, 92%; (h) IBX, DMSO:THF, 3 h, 88%; (i) 4-CH_3O–$C_6H_4CH_2P + Ph_3Cl^-$, *n*-BuLi, THF, 12 h, 0°C–rt, 70%; (j) $Pd(CH_3CN)_2Cl_2$, DCM (0.5 M), rt, 92%; (k) PPTS, MeOH, 45 °C, 12 h, 75%; (l) TBSCl, imidazole, DMAP (3 mol %), DCM, 82%; (m) MOMCl, DIPEA, DCM, rt, 90%; (n) TBAF, THF, rt, 70%.

dihydroxylation-double inversion (at C-3) sequence. A second, Sharpless asymmetric dihydroxylation[8] on **14**, with the diastereomerically matched chiral reagent AD mix-β in ^{t}BuOH–H_2O at 0 °C afforded the diol **15** in 87% yield with excellent diastereoselectivity (10:1). Unfortunately, efforts to introduce the amine functionality at C-3 always produced only the elimination product.[9]

To avoid the competitive elimination reaction, the dihydroxy ester **15** was reduced to triol **16** with $LiAlH_4$ in THF. Then, the triol **16** was subjected to regioselective 1,2-acetonide protection with 2,2-DMP in DCM using CSA to give **17** in 85% yield. Treatment of the diacetonide **17** with Tf_2O in the presence of pyridine gave triflate **18**. The sequential displacement of the triflate **18** by bromide (Bu_4NBr) followed by azide (NaN_3) provided the nitrogen function with overall retention of configuration[10] at C-3. The required five contiguous asymmetric centers at C2–C6 for the key building block **2** had now been established by the synthesis of azido compound **19**.

At this point, a one-pot deprotection–reduction–protection strategy was utilized. The azide **19** was subjected to $Pd(OH)_2/C$ catalyzed hydrogenation in the presence of $(Boc)_2O$ which effected benzyl ether deprotection, azide reduction and Boc-protection of the resulting amine to afford compound **20** in 92% overall yield. The alcohol **20** was oxidized with IBX to furnish the desired aldehyde **21** in 88% yield. For the construction of the styryl moiety of compound **3**, Wittig alkenation of the aldehyde **21** with (4-methoxyphenylmethylene) triphenylphosphorane in THF was used to provide a mixture of *E*/*Z* isomers in a ratio of 3:2 in 70% yield. Treatment of the mixture of isomers with a catalytic amount of $Pd(CH_3CN)_2Cl_2$ in 0.5 M DCM at room temperature caused isomerization[11] of the double bond and afforded the isomerically pure *E*-isomer **22** in 92% yield. The ^{1}H NMR spectrum showed a doublet at δ 6.29 ppm ($J = 15.8$ Hz) and a multiplet at 6.05–5.95 ppm which provided confirmation for the *E*-geometry.

The terminal acetonide in **22** was selectively deprotected under mildly acidic conditions (PPTS in MeOH)[12] to give the diol **23**. The two liberated hydroxyl groups were protected selectively. A TBS group was introduced regioselectively at the primary hydroxyl group to yield **24**. Introduction of methoxymethyl at the remaining free hydroxyl group was achieved by the reaction of **24** with MOMCl and diisopropylethylamine in DCM to obtain **25** in 90% yield. The conditions for the regioselective removal of the TBS protecting group from **25** were investigated next, and was possible, utilizing TBAF in THF, to provide the key fragment **2**,[13] which could be oxidized at a later stage. All these transformations completed the stereoselective synthesis of the C1–C20 segment of microsclerodermins A and B.

In conclusion, we have developed an efficient, enantioselective route for the synthesis of the C1–C20 fragment resident in microsclerodermins A and B. The route features a deoxygenative rearrangement of an alkynol, and an highly enantio- and diastereo-controled iterative

dihydroxylation as key reactions starting from *S*-(−)-citronellol. Further progress towards the total synthesis of **1** is currently ongoing in our laboratory.

Acknowledgements

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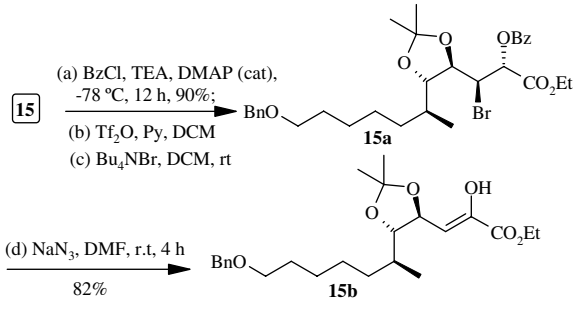
9. The introduction of the azide functionality at C-3 was planned by another asymmetric dihydroxylation-double inversion (at C-3) sequence. Unfortunately, this method resulted in the elimination product **15b**.



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13. Representative analytical data: Compound **3**: Colorless oil; $[\alpha]_D^{25}$ 31.5 (*c* 1.45, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): ^1H NMR (300 MHz, $CDCl_3$): δ 7.32–7.18 (m, 6H), 6.14–5.91 (m, 2H), 5.71 (d, 1H, $J = 15.1$ Hz), 4.45 (s, 2H), 4.13 (q, 2H, $J = 7.5$ Hz), 3.41 (t, 2H, $J = 6.0$ Hz), 2.27–2.18 (m, 1H), 1.62–1.53 (m, 2H), 1.39–1.22 (m, 9H), 1.01 (d, 3H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.0, 150.0, 145.0, 138.5, 128.2, 127.4, 127.3, 126.4, 119.2, 72.7, 70.2, 59.9, 36.9, 36.3, 29.5, 26.9, 26.1, 19.8, 14.1. ESI-MS: *m/z* 331 [M^++1]. HRMS calcd for $C_{21}H_{31}O_3$: 331.1933 (M^++1); found: 331.1926.
Compound **14**: Colorless oil; $[\alpha]_D^{25}$ −935 (*c* 0.75, $CHCl_3$). ^1H NMR (200 MHz, $CDCl_3$): δ 7.24 (m, 5H), 6.76 (dd, 1H, $J = 5.7$ Hz, $J = 4.9$ Hz), 6.02 (d, 1H, $J = 15.5$ Hz), 4.45 (s, 2H), 4.28–4.12 (m, 3H), 3.53 (t, 1H, $J = 6.5$ Hz), 3.37 (t, 2H, $J = 6.5$ Hz), 1.76–1.12 (m, 18H), 0.93 (d, 3H, $J = 7.3$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 164.9, 144.4, 137.6, 127.2, 126.4, 126.3, 121.4, 108.0, 83.7, 78.4, 71.7, 69.2, 59.3, 34.6, 31.6, 28.6, 26.0, 25.5, 25.2, 14.7, 13.0. (ESI-MS): *m/z* 427 [M^++Na]. HRMS calcd for $C_{24}H_{36}O_5Na$: 427.2563 (M^++Na), found: 427.2569.
Compound **20**: Colorless oil; $[\alpha]_D^{25}$ −1733 (*c* 0.5, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 4.99 (bs,1H), 4.04–3.98 (m, 1H), 3.84–3.81 (m, 1H), 3.76–3.71 (m, 1H), 3.62–3.57 (m, 3H), 3.60–3.40 (m, 2H), 1.70–1.13 (m, 30H), 0.96 (d, 3H, $J = 6.7$ Hz). ^{13}C NMR (75 MHz, $CDCl_3$): δ 155.7, 109.3, 109.2, 85.0, 80.0, 79.6, 79.1, 76.3, 62.7, 42.7, 35.5, 32.7, 31.3, 28.3, 27.4, 27.0, 26.7, 25.9, 16.3. (ESI-MS): *m/z* 468 [M^++Na]. HRMS calcd for $C_{23}H_{43}NO_7Na$: 468.2364 (M^++Na), found: 468.2370.
Compound **2**: Colorless oil; $[\alpha]_D^{25}$ −1073 (*c* 1.4, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.21 (d, 2H, $J = 9.0$ Hz), 6.78 (d, 2H, $J = 8.6$ Hz), 6.30 (d, 1H, $J = 15.3$ Hz), 6.06–5.96 (m, 1H), 4.94–4.89 (br s, 1H), 4.69 (s, 2H), 4.20–3.87 (m, 3H), 3.78 (s, 3H), 3.54–3.05 (m, 6H), 2.23–2.14 (m, 2H), 1.67–1.17 (m, 22H), 0.95 (d, 3H, $J = 6.0$ Hz). ^{13}C NMR (100 MHz, $CDCl_3$): δ 158.8, 130.8, 130.6, 129.1, 128.7, 126.9, 113.8, 109.3, 97.6, 83.9, 79.3, 79.2, 70.6, 68.0, 56.2, 55.2, 43.2, 36.2, 32.9, 31.2, 28.3, 27.5, 27.3, 26.5, 16.4. (ESI-MS): *m/z* 552 [M^++1]. HRMS calcd for $C_{30}H_{50}O_8N$: 552.2719 (M^++1), found: 552.2722.