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The first stereoselective total synthesis of (3*S*,4*R*)-dihydroxy-(6*S*)-undecyl-α-pyranone and total synthesis of (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide

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ABSTRACT

The first total synthesis of (3*S*,4*R*)-dihydroxy-(6*S*)-undecyl-α-pyranone **1** and total synthesis of (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxytetradecan-5-olide **2** have been achieved in five steps in a highly stereoselective manner using Maruoka allylation, olefin cross-metathesis, and Sharpless asymmetric dihydroxylation as key steps.

Marine fungi are interesting organisms from an ecological point of view, because they are significant pathogens in the marine environment.[1] Therefore, in the last decade, increased interest has been developed[2] in the chemistry of fungi isolated from the marine environment. Recently, a new metabolite (3*S*,4*R*)-dihydroxy-(6*S*)-undecyl-α-pyranone **1** was isolated from a marine-derived endophytic fungus separated from a seed of *Avicennia marina* from the mangrove of Hong Kong.[3] Its fruits are used as a Chinese medicinal herb to treat diabetes and as supplementary sources of food for humans. Later, it was also isolated from the endophytic fungus, *Ascochyta* sp.[4] from the plant Meliotus dentatus near Ahrenshoop on the Baltic Sea coast. The compound exhibits biological activity against *Microbotryum violaceum*, *Bacillus megaterium,* and *Septoria tritici* but shows the highest activity against the fungus *M. violaceum*. The stereochemistry of **1** was elucidated by the CD spectra combined with the CS Chem 3D MM2 program. HMBC and ^{1}H–^{1}H COSY spectra completely established the planar structure of **1** and protons at C-3, C-4, and C-6 all shown to be axial by analysis of their coupling constants.

In 1998, Toshima et al.[5] have isolated a new biologically active δ-lactone from *Seridium unicome* and determined its absolute configuration to be (2*S*,3*R*,5*S*)-(−)-2,3-dihydroxy-tetradecan-5-olide **2**. It exhibited positive activities such as abscisic activity against the leaves of *Chamaecyparis obtusa*, the growth inhibition against lettuce seedlings, and the antifungal activity against *Cladosporium herbarum* (see Fig. 1).

To date a nine-step single report appeared on the total synthesis of **2**[5] from *R*-malic acid, however, there are no reports on the total synthesis of **1**.

Since secondary metabolites are an important source of lead structures for new drugs, to investigate their biological activity, and in continuation of our program on the total synthesis of bio-active lactones,[6] we have initiated a short stereoselective route for the first total synthesis of **1** and also for the synthesis of **2**.

We commenced the synthesis of **1** from the commercially available dodecanal **3a** as the starting material. This aldehyde was subjected to an enantioselective Maruoka allylation[7] by treatment with titanium complex (*R*,*R*)-**I** and allyltri-*n*-butyltin to afford homoallylic alcohol **4a** in 86% yield with excellent enantioselectivity of 98% ee (determined by chiral HPLC). The alcohol **4a** was subjected to a cross-metathesis reaction,[8] using Grubbs' second

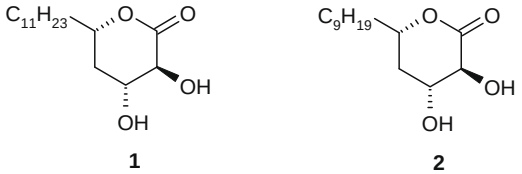

Figure 1.

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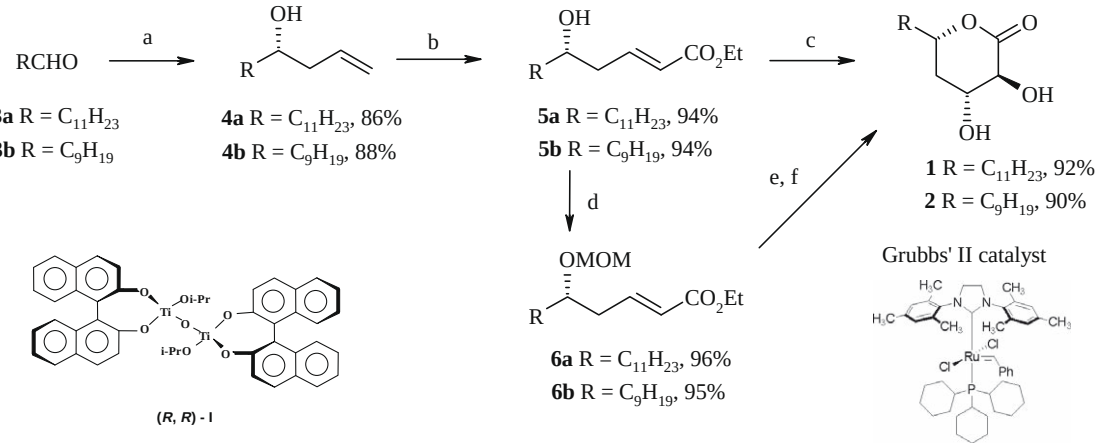

Scheme 1. Reagents and conditions: (a) (*R,R*)-I (10 mol %), *n*-$Bu_3SnCH_2CH{=}CH_2$, CH_2Cl_2, −15 °C to 0 °C, 24 h; (b) Grubb's IInd generation catalyst (5 mol %), ethyl acrylate, CH_2Cl_2, rt, 3 h; (c) AD-mix-β, *t*-BuOH/H_2O (1:1), $MeSO_2NH_2$, 0 °C, 48 h, 15% (for both **1** & **2**); (d) MOMCl, DIPEA, CH_2Cl_2, 0 °C to rt, 3 h; (e) AD-mix-β, *t*-BuOH/H_2O (1:1), $MeSO_2NH_2$, 0 °C, 24 h, 88% from **6a**, 90% from **6b** (de = 98% for both isomers); (f) $CeCl_3{\cdot}7H_2O$, CH_3CN/MeOH (1:1), reflux, 3 h.

generation catalyst and ethyl acrylate to provide α,β-unsaturated ester **5a** in 94% yield.

The asymmetric dihydroxylation of **4a** using AD-mix-β at 0 °C furnished the target lactone **1** directly in one-pot obtaining the triol, followed by lactonization. Since this reaction provides very low yield (15%) of product **1**, the secondary hydroxyl group was protected as its MOM ether. Treatment of **5a** with MOMCl in the presence of Hunig's base provided MOM ether **6a** in 96% yield. Now, the asymmetric dihydroxylation of **6a** using AD-mix-β at 0 °C was explored to generate the C-3, C-4 stereogenic centers and provided the expected diol, which on removal of MOM ether using $CeCl_3{\cdot}7H_2O$ in a mixture of MeOH/CH_3CN (1:1) at reflux furnished the target lactone **1** in good yield (92%). The spectral data of synthetic **1** were identical with those of natural **1**.[4]

After the successful completion of synthesis of **1** by very short route, we also applied the same strategy for the synthesis of **2** (Scheme 1). In a similar fashion, synthesis of **2** was commenced from the commercially available decanal **3b**. The rest of the synthesis consisted of repeating the steps as in the case of **1** and the target molecule **2** was achieved in a total of five steps, compared to the known synthesis[5] which required nine steps.

In conclusion, the first total synthesis of (3*S*,4*R*)-dihydroxy-(6*S*)-undecyl-α-pyranone **1** has been performed in only five steps from dodecanal in a highly stereoselective manner involving Maruoka allylation, olefin cross-metathesis, and Sharpless asymmetric dihydroxylation. Synthesis of **2** (analogue of **1**) was also accomplished similarly. This strategy can be favorably compared to the previous synthesis described for the compound **2**, which required up to nine steps.

Acknowledgment

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Selected spectroscopic data: compound **4a**: Colorless oil; $[\alpha]_D^{28}$ − 5.9 (*c* 1.0, $CHCl_3$); IR (neat): cm^{-1} 3365, 3078, 2926, 2858, 1640, 1462, 1128; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.87–5.72 (m, 1H), 5.15–5.07 (m, 2H), 3.64–3.55 (m, 1H), 2.32–2.22 (m, 1H), 2.16–2.05 (m, 1H), 1.47–1.23 (m, 20H), 0.89 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 135.2, 118.3, 70.4, 42.0, 36.9, 31.6, 29.6–29.3 (overlapping signals), 25.6, 22.6, 14.1 ESI MS: 266 $(M+K)^+$.
Compound **5a**: Pale yellow oil; IR (neat): cm^{-1}: 3440, 2927, 2857, 1720, 1652, 1462, 1369, 1318, 1268; ^1H NMR: ($CDCl_3$, 300 MHz) δ 6.93 (td, *J* = 15.6, 7.3 Hz, 1H), 5.86 (td, *J* = 15.6, 1.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2H), 3.72 (m, 1H), 2.43–2.24 (m, 2H), 1.49–1.21 (m, 23H) 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.5, 145.4, 123.6, 70.3, 60.3, 40.2, 37.1, 31.9, 29.6–29.3 (overlapping signals), 25.6, 22.6, 14.2, 14.1 ESI MS: 321 $(M+Na)^+$.
Compound **1**: White powder, mp: 102–104 °C; $[\alpha]_D^{28}$ − 34.2 (*c* 1.0, $CHCl_3$); IR (neat): cm^{-1} 3437, 2921, 2852, 1726, 1467, 1386, 1228, 1126, 1089; ^1H NMR ($CDCl_3$, 500 MHz) δ 4.33–4.26 (m, 1H), 4.04–3.90 (m, 2H), 2.23 (td, *J* = 13.6, 3.9 Hz, 1H), 1.82–1.70(m, 2H), 1.65–1.58 (m, 1H), 1.52–1.45 (m, 1H), 1.40–1.19 (m, 17H) 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.4, 78.5, 74.4, 69.0, 36.0, 35.7, 31.9, 29.7–29.2 (overlapping signals), 24.7, 22.6, 14.1; ESI MS: 309 $(M+Na)^+$.
Compound **4b**: Colorless oil; $[\alpha]_D^{27}$ − 7.6 (*c* 1.5, $CHCl_3$); IR (neat): cm^{-1} 3363, 3076, 2926, 2855, 1640, 1462, 1128; ^1H NMR ($CDCl_3$, 300 MHz): δ 5.87–5.72 (m, 1H), 5.15–5.06 (m, 2H), 3.64–3.55 (m, 1H), 2.34–2.22 (m, 1H), 2.16–2.05 (m, 1H), 1.47–1.23 (m, 16H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 134.9, 117.8, 70.6, 41.8, 36.7, 31.8, 29.6–29.2 (overlapping signals), 25.6, 22.6, 14.0, ESI MS: 197 $(M-1)^+$.
Compound **5b**: Pale yellow oil; IR (neat): cm^{-1} 3437, 2927, 2855, 1720, 1654, 1462, 1369, 1318, 1268; ^1H NMR: ($CDCl_3$, 300 MHz): δ 6.93 (td, *J* = 15.6, 7.3 Hz, 1H), 5.86 (td, *J* = 15.6, 1.3 Hz, 1H), 4.17 (q, *J* = 7.2 Hz, 2H), 3.76–3.67 (m, 1H), 2.43–2.24 (m, 2H), 1.70–1.56 (m, 2H), 1.50–1.19 (m, 17H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 166.4, 145.3, 123.8, 70.5, 60.3, 40.2, 37.1, 31.8, 29.6–29.3 (overlapping signals), 25.5, 22.6, 14.2, 14.1; ESI MS: 293 $(M+Na)^+$.
Compound **2**: White powder, mp: 98–100 °C; $[\alpha]_D^{27}$ − 33.4 (*c* 1, $CHCl_3$); IR (KBr): cm^{-1} 3395, 2924, 2856, 1731, 1463, 1385, 1229, 1122; ^1H NMR ($CDCl_3$, 400 MHz): δ 4.36–4.28 (m, 1H), 4.07–3.95 (m, 2H), 3.34 (br s, 1H), 2.69 (br s, 1H), 2.26 (td, *J* = 14.2, 3.8 Hz, 1H), 1.87–1.70 (m, 2H), 1.67–1.57 (m, 2H), 1.38–1.20 (m, 13H), 0.89 (t, *J* = 7.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz): δ 173.0, 78.6, 74.3, 69.2, 36.0, 35.7, 31.8, 29.7–29.2 (overlapping signals), 24.7, 22.6, 14.1; ESI MS: 299 $(M+K)^+$.