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Synthesis of (4R,5S,11R)-(-)-Cladospolide A, a Phytotoxic Macrolide from Cladosporium cladosporioides[†]

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A total synthesis of cladospolide A [(2E,4R,5S,11R)-4,5-dihydroxy-2-dodecen-11-olide] was achieved in 16 steps from ethyl (R)-3-hydroxybutanoate.

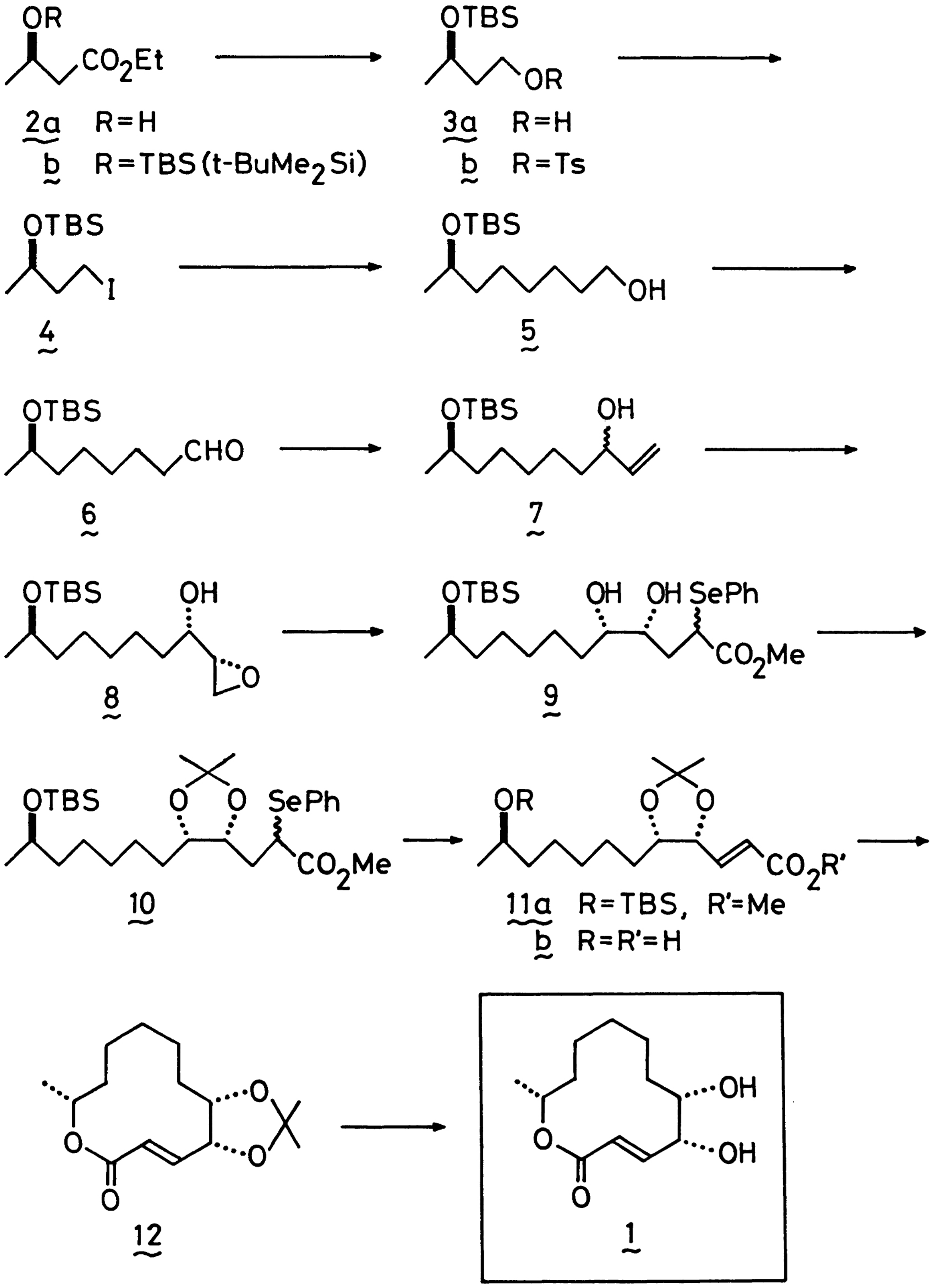
Cladospolide A is a root-growth inhibitor of lettuce seedlings produced by Cladosporium cladosporioides FI-113.[1,2] Its structure and stereochemistry were clarified as depicted in **1** [(2E,4R,5S,11R)-4,5-dihydroxy-2-dodecen-11-olide] by Hirota et al. on the basis of spectroscopic studies and X-ray analysis.[1-4] It is a 12-membered lactone with a double bond and three chiral centers, and constitutes a nice target for synthetic studies.[5] Herein we announce a total synthesis of **1** starting from ethyl (R)-3-hydroxybutanoate **2a** of microbial origin.[6]

The key-points of our synthesis as shown in the Scheme are as follows: (i) the (R)-chiral center at C-11 of **1** was derived from **2a**, (ii) the chiral centers at C-4 and C-5 were generated by employing the Sharpless asymmetric epoxidation,[7] (iii) the (E)-double bond at C-2 was introduced by applying organoselenium chemistry,[8] and (iv) the macrolactonization to **1** was achieved by the Yamaguchi method.[9]

After protecting the hydroxyl group of **2a** as t-butyldimethylsilyl ether, the resulting **2b** was reduced with lithium borohydride to give the alcohol **3a**. The corresponding tosylate **3b** was treated with sodium iodide in acetone in the presence of sodium hydrogen carbonate to furnish the iodide **4**. The chain-elongation of **4** to **5** was executed by the Grignard coupling of **4** with 4-chloromagnesiooxybutylmagnesium chloride[10] according to Normant.[11] The alcohol **5** was oxidized with pyridinium chlorochromate in dichloromethane in the presence of molecular sieves 3A[12] to afford the aldehyde **6**. Addition of vinylmagnesium bromide to **6** gave the alcohol **7** in 67% yield from **5** as a 1:1 diastereomeric mixture as revealed by the HPLC analysis of the (R)-MTPA (α-methoxy-α-trifluoromethylphenylacetic acid)[13] ester of **7**.

The Sharpless asymmetric epoxidation of **7** with t-butyl hydroperoxide and titanium tetraisopropoxide in the presence of diisopropyl L-(+)-tartrate in dichloromethane[7] gave **8**, $[\alpha]_D^{24}$ +2.7° (c 0.93, chloroform), in 25% yield from **7**. The epoxide **8** thus obtained under the condition for the kinetic resolution of **7** was 94-96% diastereomerically pure erythro-**8**. The diastereomeric ratio was deter-

[†]Dedicated to Professor Teruaki Mukaiyama on the occasion of his 60th birthday.



mined by the HPLC analysis of the (R)- and (S)-MTPA esters of **8**. The erythro-stereochemistry of **8** was supported by its later conversion to **1**. Treatment of the epoxide **8** with the dianion derived from phenylselenoacetic acid in THF at -60 °C[14] was followed by the esterification of the product with diazomethane to give crude **9**. The diol ester **9** was reacted with 2,2-dimethoxypropane and pyridinium ptoluenesulfonate[15] in dichloromethane to afford **10**, $[\alpha]_D^{24}$ -28.5° (c 0.86, chloroform), in 73.0% yield from **8**. Oxidation of the phenylselenide **10** in pyridine and dichloromethane with 35% hydrogen peroxide at -5-0 °C effected the introduction of the (E)-double bond at C-2 to give **11a**, $[\alpha]_D^{24}$ -2.8° (c 1.07, chloroform), in 90.2% yield. The genesis of the (E)-olefin **11a** by this reaction is a well-established fact originating from the preference for the less hindered transition state in the course of the syn-elimination of the selenoxide.[8] Conversion of **11a** to **11b**, the substrate for macrolactonization, was executed by treating **11a** with lithium hydroxide in THF-methanol-water followed by tetra-n-butylammonium fluoride in THF. The hydroxy acid **11b** was obtained as an oil, $[\alpha]_D^{24}$ -1.4° (c 1.3, methanol).

The mixed anhydride prepared from **11b** and 2,4,6-trichlorobenzoyl chloride was dissolved in toluene, and the solution was heated under reflux in the presence of 4-(N,N-dimethylamino)pyridine[9] to give the desired lactone **12** as an oil, $[\alpha]_D^{23}$ -18.4° (c 1.44, chloroform), in 58.6% yield after chromatographic purification over silica gel. Treatment of **12** with acetic acid-water (3:1) at 70 °C (1.25 h) gave (4R,5S,11R)-(-)-cladospolide A **1** in 82.3% yield as colorless needles, mp 92.0-92.6 °C, (lit.[2] mp 92.0-93.0 °C; mp of an authentic sample: 90-91 °C; m.mp 90-92 °C), $[\alpha]_D^{24}$ -49.3° (c 0.224, chloroform) [authentic sample: $[\alpha]_D^{24}$ -47.4° (c 0.224, chloroform)]. The spectral data of our synthetic **1**[16] were identical to those reported for the natural product.[1,2] Especially the IR and 500 MHz ^{1}H NMR spectra of the synthetic **1** were completely identical to those measured with an authentic sample of the natural **1**.

In conclusion, (4R,5S,11R)-(-)-cladospolide A was synthesized in 16 steps from ethyl (R)-3-hydroxybutanoate **2a** in 0.6% overall yield.[17]

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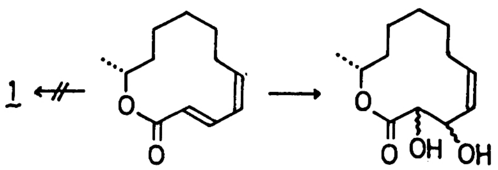
16) Spectral and analytical data of our synthetic **1** are as follows: IR (KBr) ν_{max} 3510 (s), 3380 (s), 2955 (s), 2875 (m), 1712 (vs), 1640 (m), 1460 (m), 1415 (m), 1275 (s), 1165 (s), 1125 (m), 1105 (m), 1065 (m), 1030 (m), 1000 (m), 985 (s), 880 (w) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84-0.94 (1H, m), 1.13-1.22 (1H, m), 1.28 (3H, d, J=6.5 Hz), 1.24-1.62 (6H, m), 1.64-1.72 (1H, m), 1.74-1.82 (1H, m), 2.00 (1H, d, J=6.0 Hz, OH), 2.48 (1H, d, J=3.0 Hz, OH), 3.67 (1H, m, J=6.0, 3.7, 1.5 Hz), 4.56 (1H, m), 5.13 (1H, ddq, J=6.5, 3.5, 6.5 Hz), 6.21 (1H, dd, J=16.0, 1.6 Hz), 6.81 (1H, dd, J=16.0, 5.8 Hz); ^{13}C NMR (25 MHz, $CDCl_3$) δ 19.0, 22.6, 25.1, 28.2, 30.6, 32.5, 73.0 (x2), 74.7, 122.2, 145.8, 167.9; MS m/z 229 (0.2%), 211 (1.6%), 193 (0.8%), 184 (10.1%), 127 (12.4%), 109 (19.0%), 103 (4.2%), 102 (100%, base peak), 97 (2.3%), 85 (3.9%), 84 (53.2%); CD (at 24 °C, c 0.0391, dioxan) $\Delta\varepsilon$ -3.39 (221 nm), -3.31 (240 nm); CD of an authentic sample (at 24 °C, c 0.0416, dioxan) $\Delta\varepsilon$ -3.31 (222 nm), -3.27 (241 nm); Anal. Found: C, 63.40; H, 8.88%. Calcd for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%.

17) Our attempt to synthesize **1** by oxidation of **13** with osmium tetroxide failed. Instead of **1**, an isomeric lactone **14**, mp 150.3-151.0 °C, $[\alpha]_D^{23}$ +38.6° (c 0.11, methanol), was obtained. The assigned structure was based on the lack of both an absorption at 1640 cm^{-1} in its IR spectrum and low field signals (δ 6.2-6.8) due to protons attached to the double bond conjugated with the lactonic carbonyl group. The lactone **14** showed the following spectral properties: IR (KBr) ν_{max} 3440 (s), 2960 (m), 2890 (w), 1717 (vs), 1390 (m), 1280 (s), 1238 (m), 1140 (w), 1070 (m), 1040 (m), 1010 (m), 965 (m), 740 (m) cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 1.01-1.19 (3H, m), 1.28 (3H, d, J=6.2 Hz), 1.38-1.61 (4H, m), 1.76-1.89 (1H, m), 1.96-2.05 (1H, m), 2.41-2.53 (2H, m), 2.72 (1H, d, J=6.4 Hz, OH), 4.07 (1H, dd, J=8.5, 6.4 Hz), 4.48 (1H, ddd, J=9.5, 8.5, 1.7 Hz), 5.10 (1H, ddq, J=12.2, 3.0, 6.2 Hz), 5.51 (1H, ddd, J=11.1, 9.5, 1.6 Hz), 5.56 (1H, ddd, J=11.1, 11.1, 3.7 Hz); Anal. Found: m/z 228.1367. Calcd for $C_{12}H_{20}O_4$: 228.1362.



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